

Unusual Cascade Reactions of 8-Acetoxy-6-hydroxymethyllimonene with Salicylic Aldehydes: Diverse Oxygen Heterocycles from Common Precursors

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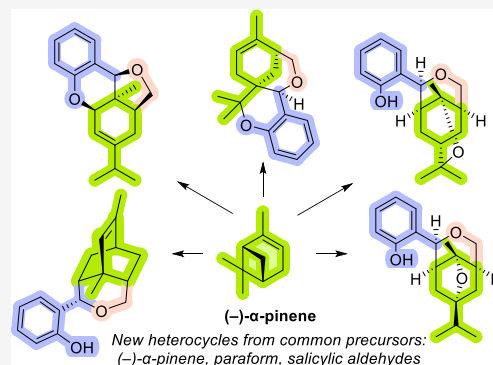


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ABSTRACT: Chiral oxygen-containing heterocyclic compounds are of great interest for the development of pharmaceuticals. Monoterpenes and their derivatives are naturally abundant precursors of novel synthetic chiral oxygen-containing heterocyclic compounds. In this study, acid catalyzed reactions of salicylic aldehydes with (–)-8-acetoxy-6-hydroxymethyllimonene, readily accessible from α -pinene, leads to the formation of chiral polycyclic products of various structural types. Three of the six isolated chiral heterocyclic products obtained from salicylic aldehyde contain previously unknown polycyclic ring types. Having carried out the reaction in the presence of Brønsted or Lewis acids (Amberlyst 15, trifluoromethanesulfonic acid, trifluoroacetic acid and boron trifluoride etherate) or aluminosilicates (montmorillonite K10, halloysite nanotubes), we found that the nature of products depends on the catalyst as well as the reaction conditions (reaction time, reactant ratio, presence or absence of solvent). Detailed mechanistic insight on the complex cascade reactions for product formation is provided with extensive experimental and quantum mechanical computational studies.



1. INTRODUCTION

Monoterpenes and their derivatives are valuable renewable raw materials in organic and polymer chemistry.^{1–3} The combination of wide availability in the enantiomerically pure forms with diverse reactivity offers an attractive starting points for various transformations, potentially leading to new chiral heterocyclic compounds with a broad spectrum of physiological activities.^{4–8} In particular, interaction of monoterpenoids and carbonyl compounds catalyzed by acidic heterogeneous aluminosilicates is an important method for synthesizing diverse oxygen-containing heterocyclic compounds.⁷

For example, (+)-3-carene **1**, one of the most abundant chiral monoterpenes, interacts with aromatic aldehydes to form compounds with 3-oxabicyclo[3.3.1]nonane **2** and isobenzofuran **3** skeletons, albeit in low yields (Scheme 1).⁹ Conversely, (+)-2-carene **4**, an isomer of terpene **1**, is significantly more reactive to electrophilic addition reactions due to the conjugation of the double bond and the cyclopropane ring. It should be noted that some isobenzofurans synthesized from carenes have neuroprotective properties^{10,11} while others can inhibit tyrosyl-DNA-phosphodiesterase I enzyme (TDP1), a promising target for therapy of oncological diseases.¹² A number of 3-oxabicyclo[3.3.1]nonenes act as antileishmanial agents^{13,14} or estrogen receptor agonists.^{15–18}

A useful strategy for monoterpene modification is their hydroxymethylation via the Prins reaction. Addition of a hydroxymethyl fragment to monoterpenes followed by subsequent reactions with aldehyde often yields unique chiral products. Since biochemical pathways are naturally stereoselective, the intrinsic chirality of such compounds may lead to promising biological activity.^{6,7}

In particular, *trans*-4-hydroxymethyl-2-carene **5** obtained via the reaction of 3-carene with formaldehyde^{19,20} reacts with aldehydes in the presence of montmorillonite clays forming oxygen-containing heterocyclic compounds. The hydroxymethyl fragment is always involved in this transformation, and the product's backbone significantly depends on the starting aldehyde's structure. The reaction of alcohol **5** with benzaldehyde leads to the mixture of isobenzofurans **6**, while interaction with salicylic aldehydes results in a cascade initiated by Prins reaction with the formation of compounds **7** with a

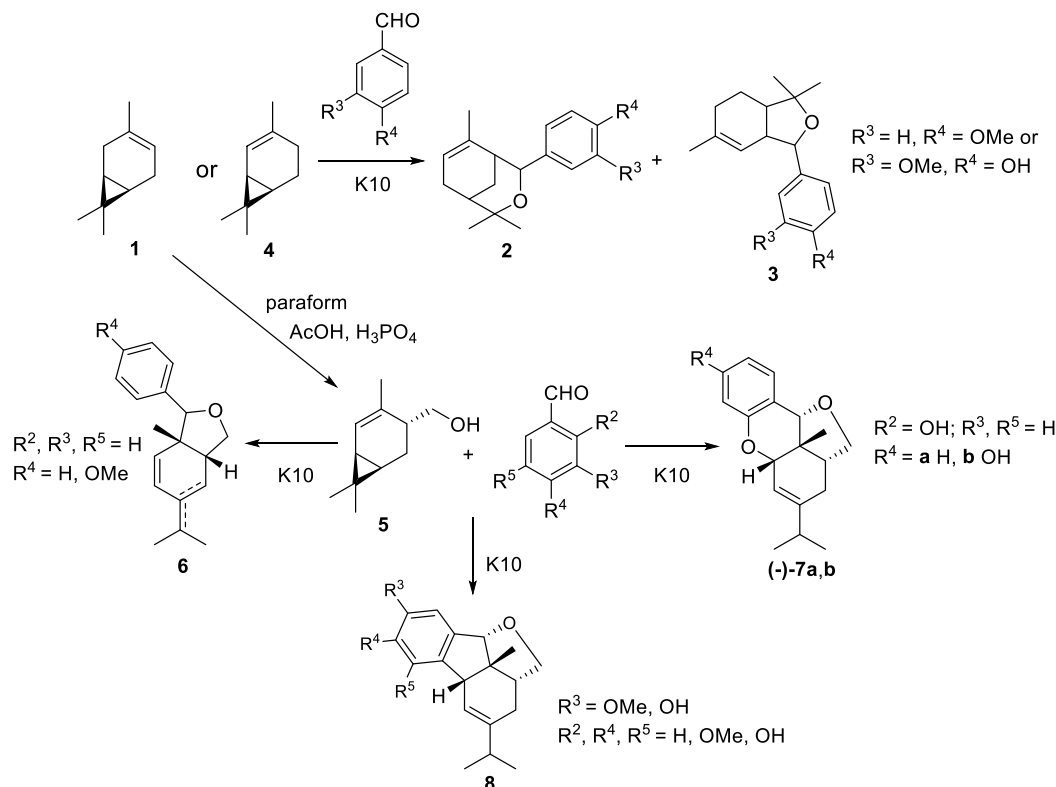
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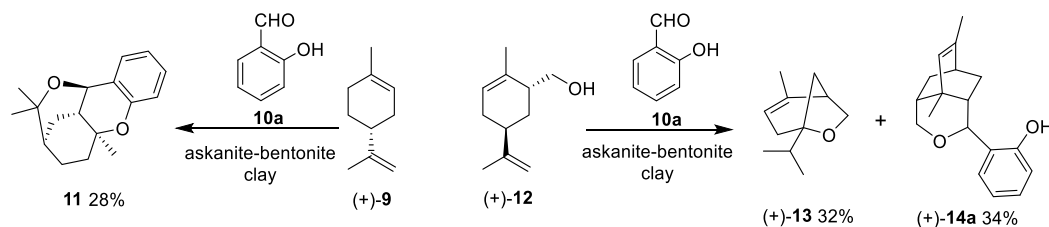
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Scheme 1. Interaction of 3-Carene 1, 2-Carene 4 and *trans*-4-Hydroxymethyl-2-carene 5 with Aromatic Aldehydes

Scheme 2. Reactions of Limonene (+)-9 and (+)-6-Hydroxymethyllimonene (+)-12 with Salicylic Aldehyde



hexahydrofuro[4,3,2-*kl*]xanthene skeleton (Scheme 1).^{7,21,22} When aldehydes containing electron-donating substituents (–OH and –OMe) are used, the cascade of Prins cyclization and subsequent intramolecular Friedel–Crafts cyclization affords hexahydrofluoreno[9,1-*bc*]furans 8. Importantly, this process requires that the electron-donating substituent is on the meta-position of the aromatic aldehyde (Scheme 1).^{7,21,23} The Prins–Friedel–Crafts cascade reaction is an effective cascade approach to synthesize complex polycyclic compounds that can strategically avoid isolation and purification of intermediates.^{21,24–27} For example, the synthesis of hexahydrofluoreno[9,1-*bc*]furans 8 from *trans*-4-hydroxymethyl-2-carene 5 is highly regio- and stereoselective, forming product 8 as a single isomer. Importantly, this product obtained by the reaction of alcohol 5 with 3-hydroxy-4-methoxybenzaldehyde (Scheme 1, $R^3 = \text{OH}, R^4 = \text{OMe}, R^5 = \text{H}$) has high cytotoxic activity (CTD₅₀ 0.9 μM) and induces apoptosis of MT-4 lymphoblastoid cells.²³

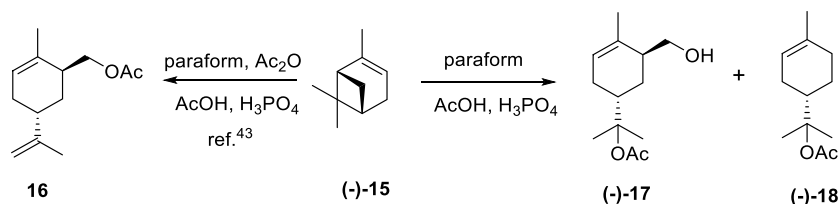
Limonene 9 is another naturally abundant monoterpene available in both enantiomeric forms from many essential oils and turpentine.^{28,29} Interaction of limonene 9 with aliphatic and aromatic aldehydes in the presence of acid catalysts has been well studied. Usually, heterocyclic products with a 3-oxabicyclo[3.3.1]nonene skeleton 2 are formed.^{7,22,30–32}

However, limonene 9 reacts with salicylic aldehyde 10a differently. The presence of a hydroxyl group in the aldehyde enables cascade transformations leading to the formation of tetracyclic compound 11 with a hydrogenated epoxymethanoxanthene skeleton (Scheme 2).²²

Currently, the only literature example of hydroxymethyl limonene derivatives interacting with aldehydes is the reaction of (+)-6-hydroxymethyl-limonene (+)-12 with salicylic aldehyde 10a, carried out in the presence of montmorillonite clay ascanite-bentonite. As a result, intramolecular heterocyclization product (+)-13 with a 6-oxabicyclo[3.2.1]octane skeleton and tricyclic compound (+)-14a with a hexahydromethaneisochrone skeleton were formed (Scheme 2).²²

Based on the ability of oxygen functionalities to stabilize cationic species and to direct their structural evolution via a combination of structural and stereoelectronic effects,^{33–42} we anticipated that reactions of hydroxymethyl limonene derivatives with aromatic aldehydes, especially those containing an ortho-hydroxy group, would be mechanistically interesting. One could anticipate a variety of one-pot cascade processes that can open synthetic access to new chiral oxygen-containing heterocyclic compounds of various structural types. The present study is the first systematic exploration of this promising area.

Scheme 3. (–)-8-Acetoxy-6-hydroxymethyllimonene (–)-17 Synthesis



Scheme 4. Reaction of (–)-8-Acetoxy-6-hydroxymethyllimonene (–)-17 and Salicylic Aldehyde 10a

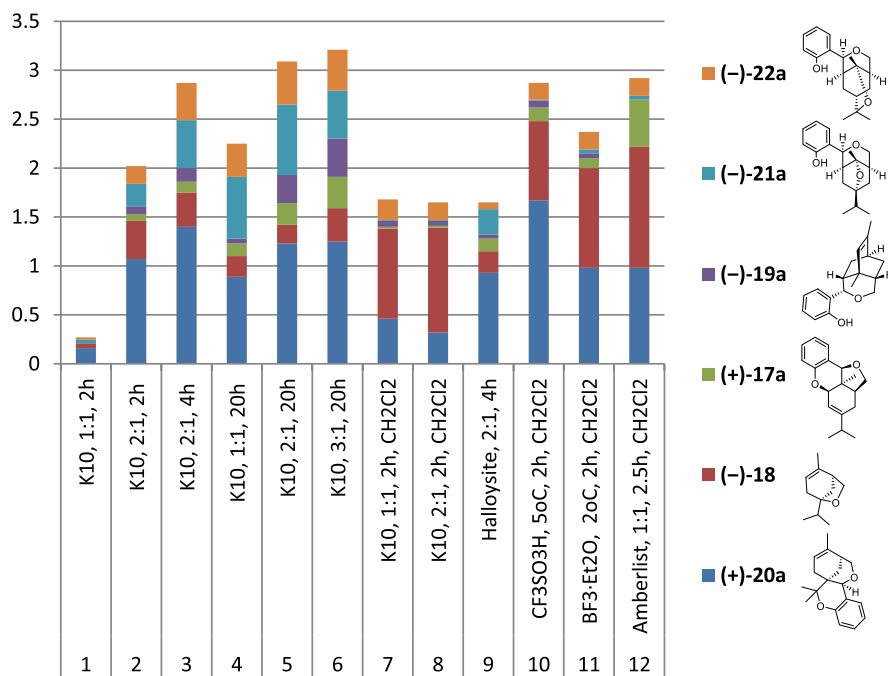
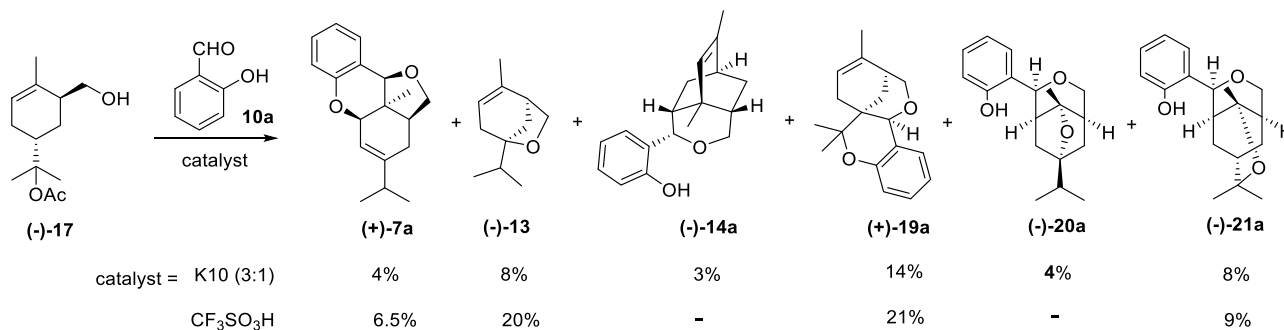


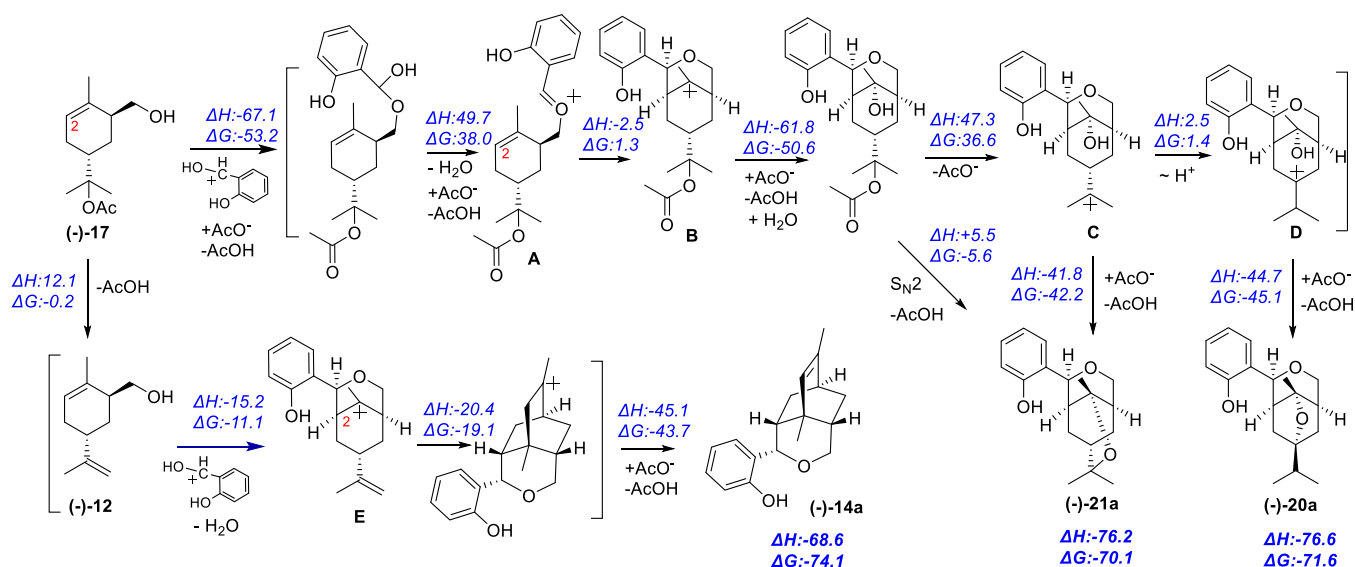
Figure 1. Composition of the reaction products in the presence of various catalysts. Montmorillonite K10 was calcined at 110 °C, acid activated halloysite nanoclay was calcined at 200 °C. Amount of catalyst and other reaction conditions see in [Experimental Section](#) and [Table S1](#).

2. RESULTS AND DISCUSSION

First, we searched for a method to synthesize hydroxymethyl limonene derivatives. We took inspiration from the earlier publication,⁴³ in which the Prins reaction starting from α -pinene 15 and paraform was carried out in the presence of acetic anhydride, glacial acetic and orthophosphoric acids at 5–15 °C. As a result, 6-hydroxymethyl-1,8(9)-*para*-menthadiene acetate 16 was obtained in 20% yield ([Scheme 3](#)).⁴³ However, under these conditions⁴³ we obtained (–)-terpinyl acetate (–)-18 as the main product ([Scheme 3](#)). Small amount of (–)-8-acetoxy-6-hydroxymethyllimonene (–)-17 we recently described⁴⁴ was formed as well. Interestingly, we did not observe formation of (–)-6-hydroxymethyllimonene (–)-12 or acetate 16. Optimal

conditions for the synthesis of 8-acetoxy-6-hydroxymethyllimonene (–)-17 were previously described by us in⁴⁴ and involved the interaction of (–)- α -pinene (–)-15 and paraform for 6 h at 8 °C in the presence of glacial acetic and orthophosphoric acids. Under these conditions, the amount of (–)-8-acetoxy-6-hydroxymethyllimonene acetate (–)-17 and (–)-terpinyl acetate (–)-18 in the reaction mixture was 20 and 35%, respectively (GC–MS data). Because acetate (–)-17 decomposes under vacuum distillation, it was isolated by Column chromatography (CC) on silica gel. The final yield of acetate (–)-17 was 19%.⁴⁴ It should be noted that direct hydroxymethylation of limonene 9 leads to the formation of a large number of compounds that, according to GC–MS data, are

Scheme 5. Computed Thermodynamic Data and Mechanism Scheme for the Experimentally Observed Products (–)-14a, (–)-20a and (–)-21a



products of the Prins reaction (more than 20 compounds with $m/z = 166, 178, 208$).

By opening synthetic access to compound 17, we made it possible, for the first time, to study its reaction with salicylic aldehyde 10a. Here we used commercially available aluminosilicate montmorillonite K10 as a catalyst, which was previously successfully employed for reaction of various monoterpenes and carbonyl compounds.^{7,9–12,20–23} The reaction was carried out in one preparative step without solvent and at room temperature. Considering that α -terpineol and limonene 9 react similarly with aldehydes in the presence of acid catalysts,⁷ one would expect similar reactivity of compounds 12 and 17. Reality turned out to be more interesting and produced unexpected new reactivity.

As a result of the interaction of (–)-8-acetoxy-6-hydroxymethylimonene (–)-17 with salicylic aldehyde 10a, six oxygen-containing heterocyclic compounds with different types of skeletons were isolated (Scheme 4). Enantiomers of the three obtained compounds, namely (+)-7a, (–)-13, (–)-14a, were described before.²² On the contrary, compound (+)-19a with a methanoxocin[3,2-*c*]chromene skeleton, compound (–)-20a with a methanofuro[3,2-*c*]pyran skeleton and compound (–)-21a with a methanopyrano[4,3-*b*]pyran skeleton were obtained for the first time. Furthermore, to the best of our knowledge, compounds with such scaffolds have not been previously described in the literature. It should be noted that we observed a reversal of the rotation sign for the compounds (+)-7a and (+)-19a relative to the starting monoterpenoid (–)-17.

Compounds (–)-20a and (–)-21a can be considered as derivatives of 1,4- and 1,8-cineoles, oxygen-containing monoterpenes which are components of essential oils of eucalyptus leaves, wormwood and other plants.^{45–47} Cineols are applied in flavor, fragrance and pharmaceutical industries.^{45–47} 1,8-Cineole is a remarkable compound that exhibits an enormous range of biological activities, including anti-inflammatory, antibacterial, antiviral, antioxidant, bronchodilatory, analgesic, and pro-apoptotic to name a few.⁴⁵ Moreover, polycyclic compounds (+)-14a and (+)-19a as well as (–)-20a and (–)-21a have a cage-like structure. Due to their polycyclic,

polychiral and complex spatial structure, natural cage-like compounds often have unique physiological activities.⁴⁸

In order to increase the yields of intermolecular reactions, we varied montmorillonite K10, acid activated halloysite nanotubes, Amberlyst 15, boron trifluoride etherate, trifluoromethanesulfonic acid and trifluoroacetic acid as catalysts. The integrations of chromatographic peaks in the reaction mixtures relative the internal standard (*n*-tridecane) are presented in Figure 1 and Table S1.

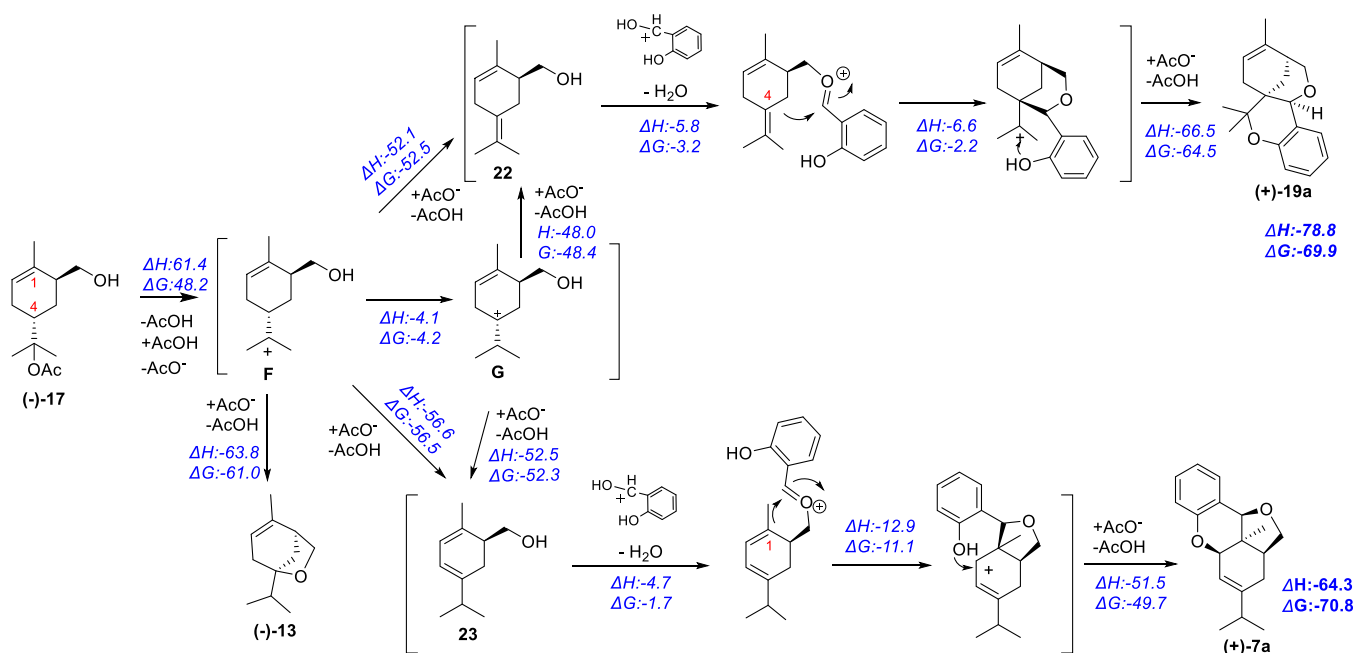
According to the obtained data (Figure 1, Table S1), compound (+)-19a with a methanoxocin[3,2-*c*]chromene scaffold is the main product, with the exception of experiments 7 and 8 where formation of the intramolecular heterocyclization product (–)-13a predominated in the presence of K10 in methylene chloride. When either $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or Amberlyst 15 were used (exp. 11 and 12), compounds (–)-13 and (+)-19a were formed in comparable quantities.

To elucidate the structure of all products, the preparative reaction was carried out at room temperature without a solvent for 20 h with montmorillonite K10 as a catalyst in an amount equal to three times the combined mass of aldehyde 10a and acetate (–)-17. Under these conditions, all minor products were formed in quantities sufficient for their isolation and structure determination. The product yields after separation of the reaction mixture by CC on silica gel were: 4% for compound (+)-7a, 8% for compound (–)-13, 3% for compound (–)-14a, 14% for compound (+)-19a, 4% for compound (–)-20a and 8% for compound (–)-21a (Scheme 4).

According to our experiments, the best way to obtain tetracyclic compound (+)-19a (selectivity 58%, according to GC–MS spectra) included the use of $\text{CF}_3\text{SO}_3\text{H}$ (25% mol, exp. 10) at 5 °C in methylene chloride. Under these conditions, the preparative yields of products after CC were: 21% for compound (+)-19a, 20% for compound (–)-13, 9% for compound (–)-21a and 6.5% for compound (–)-7a (Scheme 4). Products (–)-14a and (–)-20a were formed in this case in insignificant quantities and could not be isolated.

It should be noted that trifluoroacetic acid does not catalyze reaction of acetate (–)-17 with salicylic aldehyde 10a.

Scheme 6. Computed Thermodynamic Data and Mechanism Scheme for the Experimentally Observed Products (–)-7a, (–)-13 and (–)-19a



Thus, the ratio and composition of the products significantly depend on the nature of the catalyst, the ratio of the reagents, reaction time and the presence or absence of solvent.

2.1. Mechanistic Discussion. The interaction of (–)-8-acetoxy-6-hydroxymethylimonene (–)-17 and salicylic aldehyde 10a is a variant of Prins cyclization, a classic reaction of carbonyl compounds with unsaturated alcohols and an important method for the synthesis of heterocyclic compounds containing tetrahydropyran or tetrahydrofuran moieties.^{49,50} The reaction begins with oxocarbenium cation A, which is formed after the attack of the hydroxyl group of compound (–)-17 on the carbonyl carbon atom of the protonated aldehyde, proton transfer and elimination of water (Scheme 5). Subsequent carbocyclization at position 2 in the intermediate cation A leads to cation B. Next, addition of a water molecule and elimination of the acetate group makes the intermediate carbocations C and D. These cations can be intercepted by intramolecular heterocyclization to produce (–)-21a and (–)-20a (Scheme 5). The overall transformation is highly exergonic and the majority of calculated intermediate steps are thermodynamically feasible. Although the formation of cation C via the loss of acetate anion is significantly endergonic, this penalty can be greatly alleviated if the leaving acetate group is protonated, which is certainly possible at the reaction conditions. Alternatively, a direct S_N2 route can avoid the formation of carbocation on the way to (–)-21a. Note that a 1,2-hydride shift is needed to connect the starting materials with the isomeric product (–)-20a.

Compound (–)-14a, which is also the product of the oxocarbenium cation addition at position 2, is likely to form after the conversion of alcohol (–)-14a into alcohol (–)-12 and then to carbocation E. Synthesis of compound 14a from alcohol 12 and salicylic aldehyde 10a was described by us earlier.²²

The formation of compounds (+)-7a and (+)-19a should proceed via the intermediate formation of dienols 22 and 23. Both of them can interact with a protonated aldehyde molecule to initiate a sequence of two cyclizations leading to the

tetracyclic compounds (+)-19a and (+)-7a. Addition to the carbonyl carbon occurs at the fourth and first positions of the starting acetate (–)-17, respectively (Scheme 6).

Computational analysis for these reaction mechanisms is a difficult task since the starting compound (–)-17 contains several reactive centers and, moreover, apparently turns into dienols during the reaction, which may also have multivariant reactivity. As a result, many reaction pathways could coexist making this system very complex for theoretical analysis. Nevertheless, in the Schemes 5 and 6 we show the computationally calculated energies for the experimentally observed products. All structures were fully optimized with Gaussian 16 at the M06-2X/6-31+G(d,p)/GD3/UF/SMD=DCM level of theory. Quantum chemical calculations revealed (Schemes 5 and 6) that there was no significant difference between the energy of products. The lack of a clear thermodynamic favorite could explain the low selectivity of the reaction.

Computational analysis of the isomeric ions and dienols which may form from acetate (–)-17 under the acidic conditions prior to interaction with aldehyde 10a indicates that the allylic cation I is the most stable of the choices presented in Figure 2. Interestingly, the starting cation F is the least stable, in agreement with its high reactivity. Due to their instability, cations are very reactive and can quickly undergo rearrangements into more stable products. Cation J was so inherently unstable, that it consistently rearranged into G or H in silico irrespective of the computational methodology (Figure 2). Compounds 22 and (–)-12 are the least stable dienols. This finding agrees well with the observation that they are not produced in appreciable amounts under the experimental conditions. However, dienol 22 is the precursor for the major product (+)-19a, so it is likely to form as a transient reactive species (Figure 2).

To check if proposed dienol intermediates (–)-12, 22 and 23 can really be involved in transformations, we tried to obtain these compounds from (–)-17. We found that incubation of (–)-17 in the presence of K10 or triflic acid led to formation of

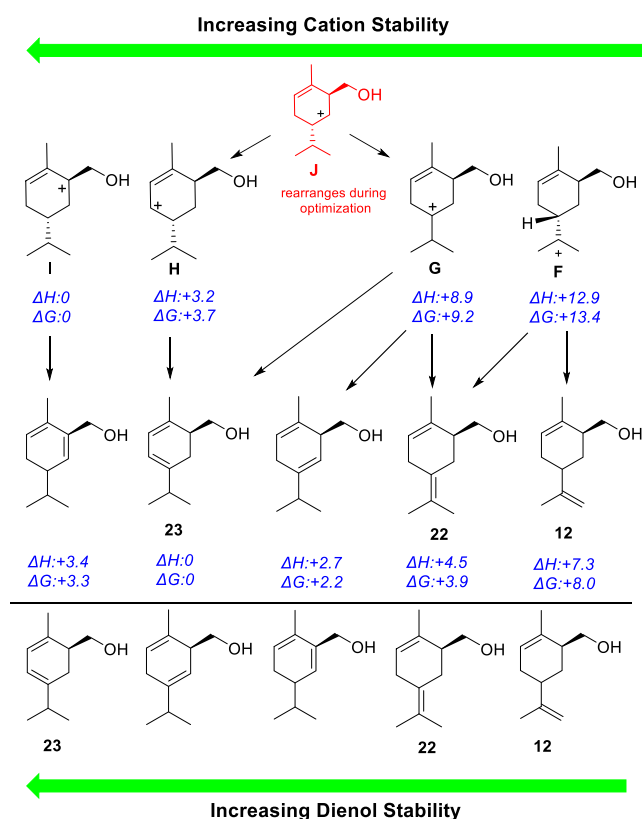


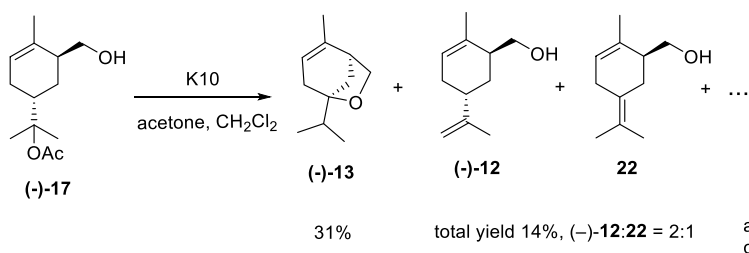
Figure 2. Comparison of cation and dienols stability (kcal/mol).

compound (–)-13. The problem was solved by addition of acetone in the reaction mixture. Apparently, the ketone can mimic the species formed in the interaction of salicylic aldehyde with the catalyst but cannot react with (–)-17 in these conditions.

Thus, transformation of acetate (–)-17 in the presence of montmorillonite K10 and acetone in CH₂Cl₂ after 2 h led to the formation of complex mixture of products including compound (–)-13 (the main product) and 6-hydroxymethyl-*p*-menthadienes (–)-12 and 22 (Scheme 7). Compound 23 formation was not observed in this reaction. We did not manage to isolate compounds (–)-12 and 22 individually using silica gel CC, only mixtures of these products were obtained. Mixtures of (–)-12 and 22 in a ratio of 5:1 and 1:1 were used for further reactions.

Interaction of (–)-12 and 22 mixtures and salicylic aldehyde in the presence of montmorillonite K10 were carried out in CH₂Cl₂ (Scheme 8, Table 1, exp. 1 and 2) and without solvent (exp. 3 and 4). After 1 h the reactions were quenched by addition of ethyl acetate and filtration of the catalyst. Content of reaction mixture components is presented in Table 1.

Scheme 7. Transformation of Acetate (–)-17



Considering the results of reactions 1 and 2 (Table 1, in CH₂Cl₂), one can conclude that compound (–)-12 is converted mainly into the intramolecular heterocyclization product (–)-13, and to a lesser extent, into products (–)-14a and (–)-21a. Under the same conditions, compound 22 transformed into ester (–)-13 and apparently degrades (oligomerization, polymerization processes).

When the reactions were carried out without solvent (Table 1, exp. 3, 4), compound (–)-12 is converted mainly into the product (–)-14a, and to a lesser extent into the products (–)-13, (+)-19a and (–)-21a. Under the same conditions, the main direction of product 22 transformation is the formation of compound (+)-19a. Compound 22 is consumed faster than compound (–)-12, which also improves selectivity for product (+)-19a.

These data are consistent with the proposed reaction mechanisms of (–)-17 acetate and salicylic aldehyde 10a, as well as with the literature data for the reaction of dienol (+)-12.

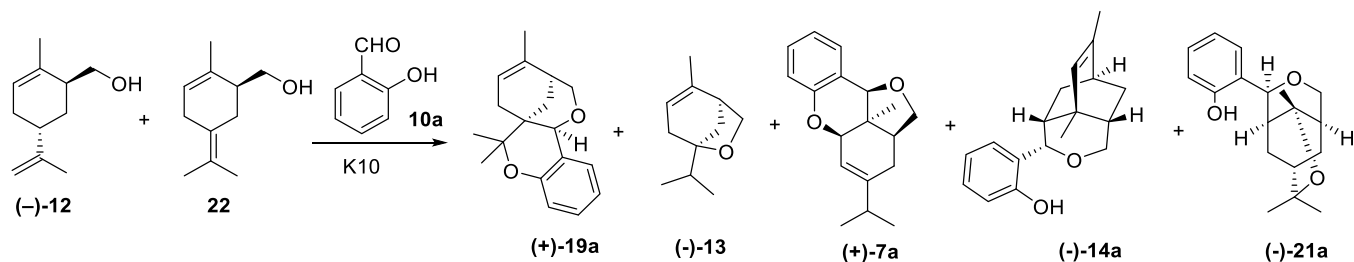
It should be noted that there we did not identify compound (–)-20a in all these reaction mixtures. Moreover, when compounds (–)-12 and 22 reacted with the salicylic aldehyde, formation of unknown products was observed.

To evaluate the nature of the experimentally unidentified reaction pathways, we surveyed thermodynamic stability of the possible products that can form from the interaction of dienols with salicylic aldehydes in reaction pathways that proceed via tertiary carbocations (Schemes 9 and S1).

In carbocationic reactions, the barriers are generally low, so reactions have an easier time to find suitable thermodynamic minima. Although the structural constraints imposed by the polycyclic structures can build kinetic traps and interrupt cascade transformations at intermediate structures,^{34,35} we will limit this analysis to only thermodynamics. In the presence of powerful strongly acidic catalysts, kinetic barriers are likely to be sufficiently small and sometimes irrelevant as the carbocationic transformations maybe controlled by post-transition state bifurcations.^{S1–S3}

Gratifyingly, the experimentally observable compounds (+)-19a and (–)-14a are heavily thermodynamically favored. However, computational analysis indicates that several of the proposed structures are also thermodynamically favorable relative to the starting materials and may be accessible in the future if proper catalysts and conditions for their formation are identified. It should be noted that although these products are thermodynamically favorable to form, under these reaction conditions, they will likely be outcompeted and interconverted into the more stable products that were isolated experimentally. The fact that the diastereomer of 19a was not isolated despite the higher thermodynamic favorability indicates that this reaction is stereospecific.

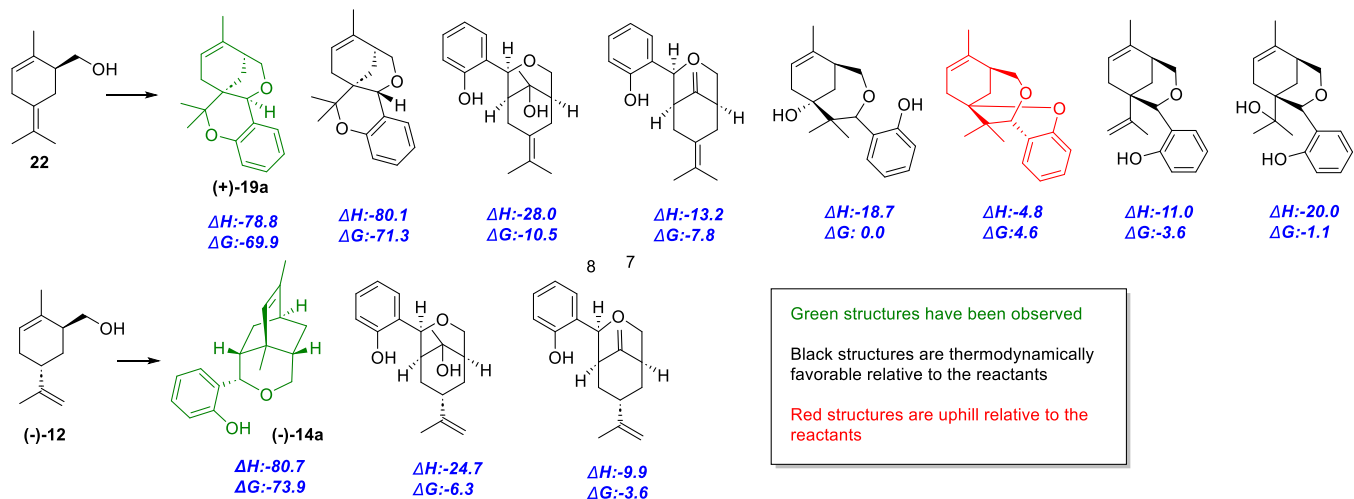
Scheme 8. Reactions of (–)-12 and 22 with Salicylic Aldehyde 10a

Table 1. Interaction of (–)-12 and 22 Mixtures with Salicylic Aldehyde^a

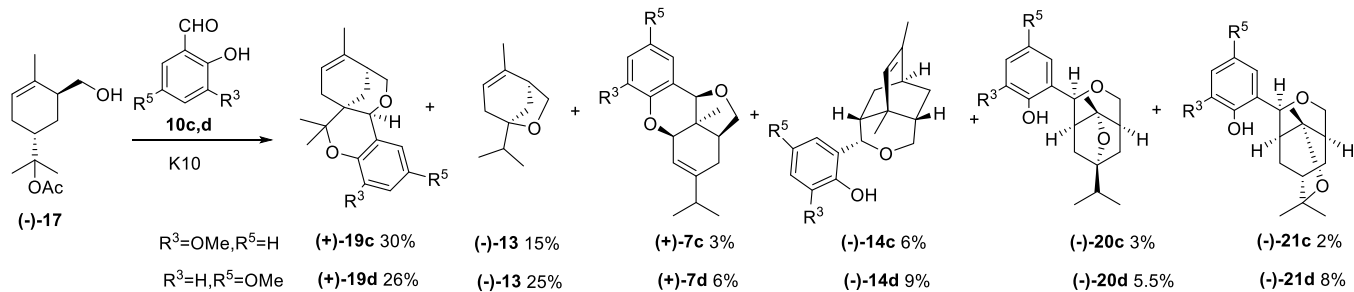
N	(–)- 12:22	Solvent	Content of the reaction mixture (GC-MS), %						
			(–)-12	22	(+)-19a	(–)-13	(+)- 7a	(–)- 14a	(–)- 21a
1	5:1	CH ₂ Cl ₂	-	-	-	55.6	4.2	20.8	9.9
2	1:1	CH ₂ Cl ₂	73.9	14.9	1.6	8.9	-	0.82	-
3	5:1	-	-	-	8.9	11.1	3.2	48.5	5.0
4	1:1	-	13.6	-	40.7	5.1	2.3	5.7	0.86

^aK10: [(–)-12 + 22] + aldehyde 10a = 2 by weight, R.T., 1 h, K10 calcined for 3 h at 105 °C. ^bUnidentified compounds, *m/z* 270, 288.

Scheme 9. Additional Possible Products from the Reactions of Salicylic Aldehyde with (–)-12 and 22



Scheme 10. Interaction of Acetate (–)-17 with Aldehydes 10c and 10d



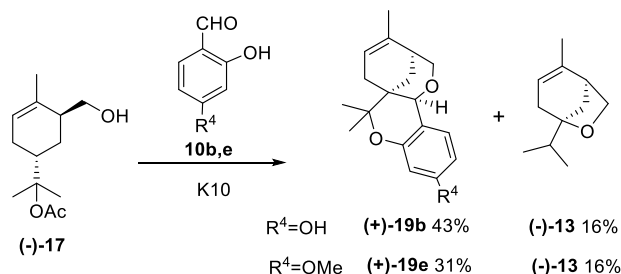
2.2. Reaction Scope. The interactions of (–)-8-acetoxy-6-hydroxymethylmonene (–)-17 with salicylic aldehydes **10c** and **10d** containing methoxy groups in meta-position catalyzed by montmorillonite K10 proceed similarly to the reaction with aldehyde **10a**, forming six products (Scheme 10).

Thus, condensation of acetate (–)-17 and 2-hydroxy-3-methoxybenzaldehyde **10c** leads to the formation of the methanoxocin[3,2-*c*]chromene derivative (+)-19c as the main product in 30% yield. The yield of intramolecular heterocyclization product (–)-13 was 15% whereas the minor products (+)-7c, (–)-14c, (–)-20c and (–)-21c were formed in low yields (2–6%) (Scheme 10).

In the interaction of acetate (–)-17 with 2-hydroxy-5-methoxybenzaldehyde **10d**, an increase in the yields of minor products (+)-7d, (–)-14d, (–)-20d and (–)-21d was observed. The yields of methanoxocin[3,2-*c*]chromene (+)-19d and compound (–)-13 were 26 and 25%, respectively (Scheme 10).

The reactions of acetate (–)-17 with salicylic aldehydes containing donor substituents in para-position, 2,4-dihydroxybenzaldehyde **10b** and 2-hydroxy-4-methoxybenzaldehyde **10e**, proceed somewhat differently. As a result of the reaction of acetate (–)-17 and 2,4-dihydroxybenzaldehyde **10b**, two products were formed: compound (+)-19b with a methanoxocin[3,2-*c*]chromene skeleton and compound (–)-13, which were isolated with the yields of 43 and 16%, respectively. Similarly, the monoterpene (–)-17 reacts with 2-hydroxy-4-methoxybenzaldehyde **10e** to form the products (+)-19e and (–)-13 in the yields of 31 and 16%, respectively (Scheme 11).

Scheme 11. Interaction of Acetate (–)-17 with Aldehydes **10b and **10e****



Thus, the main direction of the formation of condensation products of (–)-8-acetoxy-6-hydroxymethylmonene (–)-17 and salicylic aldehydes **10** containing additional hydroxy or methoxy groups is the formation of methanoxocino[3,2-*c*]chromenes **19**, and the selectivity depends on the position of the substituents.

2.3. Structure Elucidation of Reaction Products. Structures of all products were determined by using 1D and 2D NMR experiments data (HSQC, HMBC, COSY and NOESY), HR-MS analysis (see Materials and Methods and Supporting Information). In addition, we were able to isolate single crystals of compounds (+)-19d and (–)-21a through recrystallization from ethyl acetate–hexane 1:1 mixture by slow evaporation of solvent at atmospheric pressure and room temperature. Subsequent X-ray diffraction analysis confirmed the new types of cyclic structures, i.e., methanoxocin[3,2-*c*]chromenes **19** and methanopyrano[4,3-*b*]pyrans **21** (Figure 3).

For compounds with the methanofuro[3,2-*c*]pyran skeleton (–)-20 the presence of a cyclized tetrahydropyran structure is

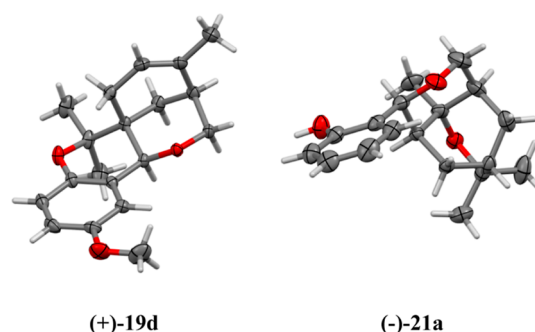


Figure 3. Molecular structure of (+)-19d (CCDC 2353259) and (–)-21a (CCDC 2353260) according to X-ray data.

confirmed by the HMBC cross-peaks C4–H2. The presence of cross-peaks H2–H1, H2–H4 and H2–H10 in compound (–)-20a NOESY spectrum indicates that these protons have *cis*-orientation to each other and in relation to the tetrahydropyran ring. Despite careful proton assignment in previously published NMR data for compound (+)-14a,²² it could not fully identify the location of the aromatic substituent. From the presence of H4–H13 cross peaks in NOESY spectra of bicyclo[2.2.2]octene derivatives (–)-14a–c, the *endo*-position of the aromatic substituent can be determined. Spatial structure of compounds (+)-7 with hexahydrofuro[4,3,2-*kl*]xanthene scaffold is confirmed by the presence of H1–H16, H5–H16, H8–H16 NOESY peaks.

3. CONCLUSIONS

In summary, reaction cascades mediated by the Prins reactions of a new monoterpene derivative (–)-8-acetoxy-6-hydroxymethylmonene (–)-17 with salicylic aldehydes were studied for the first time. The reaction of salicylic aldehyde **10a** with acetate (–)-17 forms six chiral heterocyclic products, with three previously unknown polycyclic ring types. Hence, the new monoterpene derivative (–)-17 is a promising precursor for new chiral polycyclic compounds with potential biological activity. Plausible mechanisms for product formation were discussed in detail and are supported with experimental and computational studies.

Overall, these transformations illustrate how high energy functionalities (the alkenes) can provide the driving force for the multistep transformations where the alkene π -bonds are transformed into σ -bonds in the cyclic products. The presence of oxygen is essential as well as it provides stereoelectronic stabilization to the multiple electron deficient intermediates.³³ The exact downhill trajectories for navigating these complex energy landscapes are tunable by the nature of catalyst and other external factors.

4. EXPERIMENTAL SECTION

4.1. Materials and Methods. All reagents and solvents are commercially available and used as supplied. Montmorillonite K10 (Aldrich) was calcined at 105 °C for 3 h immediately before use. Halloysite nanoclay (Aldrich) was prepared according to⁵⁴ and was calcined at 200° for 2 h immediately before use. CH₂Cl₂ was passed through calcined Al₂O₃. (–)-8-Acetoxy-6-hydroxymethylmonene (–)-17 have been synthesized according to⁴⁴ from (–)- α -pinene (98.0%, Aldrich). CC: silica gel (SiO₂; 60–200 μ ; Macherey-Nagel); hexane/EtOAc 100:0 $\rightarrow$ 0:100.

Analytical and spectral measurements were acquired at the Multi-Access Chemical Research Center SB RAS, located in Novosibirsk, Russia. GC/MS (purity control and products analysis): Agilent 7890A

(Agilent Technologies, Santa Clara, CA, USA) with a quadrupole mass spectrometer Agilent 5975C as a detector, HP-5MS quartz column, 30,000 × 0.25 mm, He (1 atm) as carrier gas. Optical rotation: polAAR 3005 spectrometer (Optical Activity LTD, Huntingdon, UK), CHCl₃ soln. HR-MS: DFS-Thermo-Scientific spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) in a full scan mode (15–500 *m/z*, 70 eV electron-impact ionization, direct sample introduction). GC–MS (purity control and products analysis): Agilent 7890A (Agilent Technologies, Santa Clara, CA, USA) with a quadrupole mass spectrometer Agilent 5975C as a detector, HP-5MS quartz column, 30000 × 0.25 mm, He (1 atm) as the carrier gas. ¹H and ¹³C NMR: Bruker Avance-III 600 (Bruker Corporation, Karlsruhe, Germany) apparatus at 600.30 MHz (¹H) and 150.95 MHz (¹³C), Bruker DRX-500 (Bruker Corporation, Karlsruhe, Germany) apparatus at 500.13 MHz (¹H) and 125.76 MHz and Bruker Avance 400 (Bruker Corporation, Karlsruhe, Germany) apparatus 400.13 MHz (¹H) and 100.61 MHz (¹³C). Spectra were recorded in CDCl₃, chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) in Hz. Structural assignments were made with additional information from gCOSY, gNOESY, gHSQC, and gHMBC experiments.

Note that numeration of compounds atoms is given for assigning the signals in the NMR spectra and does not coincide with that for the names according to the nomenclature of compounds (see [Supporting Information](#)).

4.2. Safety Statement. There are no any specific hazards or risks associated with the reported work that require preventative measures beyond those commonly expected to be present in a laboratory setting.

4.3. General Procedure. An appropriate aldehyde **10** (1 equiv) was added to a suspension of montmorillonite K10 in CH₂Cl₂ (20 mL). A solution of (–)-8-acetoxy-6-hydroxymethylimonene (–)-**17** (1 equiv) in CH₂Cl₂ (5 mL) was added. The solvent was distilled off, and the reaction mixture was left at room temperature for 20 h. Following this, 20 mL of ethyl acetate and 20 mL acetone was added, the catalyst was separated by filtration, and the resulting filtrate was subjected to evaporation. The residue was purified by CC on SiO₂.

4.3.1. Reaction of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17** and Salicylic Aldehyde **10a**.** **4.3.1.1. In the Presence of Montmorillonite K10.** The reaction (according to general procedure (GP)) of salicylic aldehyde **10a** (0.81 g, 6.6 mmol, 1 equiv), acetate (–)-**17** (1.50 g, 6.6 mmol, 1 equiv) in the presence of K10 (6.9 g) gave compounds (+)-**7a** (0.065 g, 4%), (–)-**13** (0.088 g, 8%), (–)-**14a** (0.050 g, 3%), (+)-**19a** (0.245 g, 14%) and mixture of compounds (–)-**20a** and (–)-**21a** (0.225 g, (–)-**21a**/(–)-**20a** = 1.9, 12%). Compound (–)-**21a** was isolated in individual form by further CC on SiO₂.

4.3.2. (3*S*,6*aR*,12*bR*)-4,7,7-Trimethyl-3,6-dihydro-2*H*,7*H*,12*bH*-3,6a-methanooxocino[3,2-*c*]chromene (+)-19a**.** A white waxy compound; [α]_D²⁶ +66 (c 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 7.41 (1H, dm, *J*_{15,14} = 7.4 Hz, H15), 7.11–7.18 (1H, m, H13), 6.92–6.86 (1H, m, H14), 6.74 (1H, dd, *J*_{12,13} = 8.2 Hz, *J*_{12,14} = 1.2 Hz, H12), 5.45–5.52 (1H, m, H5), 4.47 (1H, s, H1), 3.87 (1H, dm, ²*J* = 11.0 Hz, H2'), 3.76 (1H, dd, ²*J* = 11.0 Hz, *J*_{2,3} = 2.1 Hz, H2), 2.30 (1H, dm, ²*J* = 19.0 Hz, H6'), 2.09–2.16 (1H, m, H3), 1.83 (1H, dm, ²*J* = 19.0 Hz, H6), 1.76 (1H, dm, ²*J* = 11.6 Hz, H8'), 1.69–1.74 (3H, m, Me16), 1.64 (1H, dd, ²*J* = 11.6 Hz, *J*_{8,3} = 3.2 Hz, H8), 1.33 (3H, s, Me18), 1.28 (3H, s, Me17). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 152.5 (s, C11), 134.1 (s, C4), 128.5 (d, C13), 126.8 (d, C15), 123.6 (d, C5), 121.8 (s, C10), 120.2 (d, C14), 116.2 (d, C12), 80.8 (s, C9), 78.7 (d, C1), 69.4 (t, C2), 36.7 (d, C3), 35.2 (s, C7), 31.2 (t, C8), 27.5 (t, C6), 23.1 (q, C18), 22.2 (q, C17), 21.7 (q, C16). HRMS *m/z*: [*M*]⁺ calcd for C₁₈H₂₂O₂, 270.1614; found, 270.1613.

4.3.3. 2-((3*S*,4*aS*,5*S*,8*R*,8*aR*)-2,2,8*a*-Trimethylhexahydro-2*H*,5*H*-3,8-methanopyrano[4,3-*b*]pyran-5-yl)phenol (–)-21a**.** White powder; mp 100.4 °C with decomposition; [α]_D²⁶ –32 (c 0.3, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 8.69 (1H, s, OH), 7.10–7.17 (1H, m, H17), 6.90 (1H, dd, *J*_{19,18} = 7.7 Hz, *J*_{19,17} = 1.6 Hz, H19), 6.77–6.86 (2H, m, H16, H18), 4.91 (1H, s, H2), 3.83 (1H, dd, ²*J* = 11.4 Hz, *J*_{4,5} = 1.8 Hz, H4'), 3.76 (1H, dd, ²*J* = 11.4 Hz, *J*_{4,5} = 2.0 Hz, H4), 2.21–2.32 (1H, m, H6'), 2.09–2.18 (1H, m, H1), 1.88–1.99 (1H, m, H8'), 1.80 (1H, dm, *J*_{5,6} = 11.2 Hz, H5), 1.49–1.60 (3H, m, H-6, H7, H8), 1.32

(3H, s, Me10), 1.24 (3H, s, Me13), 1.21 (3H, s, Me12). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 156.6 (s, C15), 128.5 (d, C17), 126.2 (d, C19), 122.9 (s, C14), 119.4 (d, C18), 117.2 (d, C16), 80.7 (d, C2), 72.3 (s, C11), 70.6 (t, C4), 70.2 (s, C9), 41.7 (d, C1), 36.4 (d, C5), 33.1 (d, C7), 28.8 and 28.7 (2q, C12, C13), 27.1 (t, C6), 23.8 (t, C8), 23.0 (q, C10). HRMS *m/z*: [*M*]⁺ calcd for C₁₈H₂₄O₃, 288.1720; found, 288.1723.

4.3.4. 2-((2*R*,3*aS*,4*S*,7*R*,7*aR*)-2-Isopropyl-7*a*-methylhexahydro-4*H*-2,7-methanofuro[3,2-*c*]pyran-4-yl)phenol (–)-20a**.** The NMR spectra of compound (–)-**20a** was recorded for its mixture with compound (–)-**21a** in the ratio (–)-**20a**/(–)-**21a** = 1.9:1. ¹H NMR (CDCl₃, 600 MHz): δ 8.40 (1H, s, OH), 7.16–7.11 (1H, m, H17), 6.93–6.90 (1H, m, H19), 6.85–6.79 (2H, m, H16, H18), 4.67 (1H, s, H2), 4.09 (1H, br.d, ²*J* = 11.9 Hz, H4'), 3.65 (1H, dd, ²*J* = 11.9 Hz, *J*_{4,5} = 1.8 Hz, H4), 2.30–2.25 (1H, m, H1), 2.00 (1H, sept, *J*_{11,12} = *J*_{11,13} = 6.9 Hz, H11), 1.95–1.84 (2H, m, H5, H6'), 1.72–1.66 (1H, m, H8'), 1.62–1.58 (2H, m, H6, H8), 1.49 (3H, s, Me10), 0.911 and 0.905 (6H, 2d, *J*_{12,11} = *J*_{13,11} = 6.9, Me12, Me13). ¹³C{¹H} NMR (CDCl₃, 151 MHz): δ 155.9 (s, C15), 128.6 (d, C17), 126.1 (d, C19), 124.1 (s, C14), 119.5 (d, C18), 117.0 (d, C16), 88.3 (s, C7), 80.6 (s, C9), 78.1 (d, C2), 67.3 (t, C4), 47.6 (d, C1), 42.7 (d, C5), 37.3 (t, C6), 34.3 (t, C8), 32.7 (d, C11), 18.1 (q, C10), 17.93 and 17.86 (2q, C12, C13). HRMS *m/z*: [*M*]⁺ calcd for C₁₈H₂₄O₃, 288.1720; found, 288.1723.

Spectral characteristics of compounds (+)-**7a**, (–)-**13** and (–)-**14a** correspond to those published previously.²²

4.3.5. (2*aS*,2*a*¹*S*,5*aR*,10*bS*)-4-Isopropyl-2*a*1-methyl-2,2*a*,2*a*¹,3,5*a*,10*b*-hexahydrofuro[4,3,2-*kl*]xanthene (+)-7a**.** Colorless oil; [α]_D²⁶ +12 (c 0.2, CHCl₃).

4.3.6. (1*S*,5*S*)-5-Isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (–)-13**.** Colorless oil; [α]_D²⁶ –13 (c 0.7, CHCl₃).

4.3.7. 2-((1*R*,4*S*,4*aR*,7*S*,8*aR*)-4*a*,6-Dimethyl-3,4,4*a*,7,8,8*a*-hexahydro-1*H*-4,7-methanoisochromen-1-yl)phenol (–)-14a**.** Colorless oil; [α]_D²⁶ –38 (c 0.2, CHCl₃).

4.3.8. Interaction of 8-Acetoxy-6-hydroxymethylimonene (–)-17** with Salicylic Aldehyde **10a** in the Presence of Various Acid Catalysts.**

- Without Solvent: To a suspension of montmorillonite K10 in 1 mL of CH₂Cl₂ a solution of salicylic aldehyde **10a** (0.054 g, 0.44 mmol) in 1 mL of CH₂Cl₂, *n*-tridecane (54 μ L) was added. After that, solution of acetate (–)-**17** (0.100 g, 0.44 mmol) in 1 mL of CH₂Cl₂ was added. The solvent was distilled off. The reaction mixture was kept at room temperature depending on the experimental conditions. Ethyl acetate was added, and the clay was filtered. The resulting solution was analyzed by GC–MS (conditions and results, see [Table S1](#)).
- In the Presence of a Solvent: Catalyst was added to a solution of salicylic aldehyde **10a** (0.054 g, 0.44 mmol), *n*-tridecane (54 μ L), acetate (–)-**17** (0.100 g, 0.44 mmol) in 10 mL CH₂Cl₂. The reaction mixture was stirred depending on the experimental conditions. Wash with an aqueous solution of NaHCO₃, dry with Na₂SO₄. The resulting solution was analyzed by GC–MS (conditions and results, see [Table S1](#)).

4.3.8.1. In the Presence of CF₃SO₃H (25% mol.). Solution of salicylic aldehyde **10a** (0.40 g, 3.3 mmol) and acetate (–)-**17** (0.75 g, 3.3 mmol) in 80 mL CH₂Cl₂ was cooled to 5 °C. Then CF₃SO₃H (73 μ L) was added and stirred at 5 °C for 2 h. Reaction mixture was washed with a saturated aqueous solution of NaHCO₃, water, and dried the solution with Na₂SO₄. The desiccant was filtered off the solution was evaporated, the residue was separated by CC on SiO₂ with EtOAc/hexane gradient (0–100%) to obtain compounds (+)-**7a** (0.058 g, 6.5%), (–)-**13** (0.110 g, 20%), (+)-**19a** (0.190 g, 21%) and compound (–)-**21a** (0.086 g, 9%).

4.4. Transformations of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17** in the Presence of Acetone and K10 in CH₂Cl₂.** To solution of (–)-8-acetoxy-6-hydroxymethylimonene (–)-**17** (2.00 g, 8.9 mmol) and acetone (0.50 g, 8.6 mmol) in CH₂Cl₂ (60 mL) montmorillonite K10 was added (2.00 g). The reaction mixture was stirred at room temperature for 2 h. Then catalyst was separated by filtration. The solvent was distilled off; the residue was separated by CC on SiO₂ to yield compound (–)-**13** (0.461 g, 31.4%), mixture of

compounds (–)-**12** and **22** (5:1, 0.103 mg, total yields 7.0%) and mixture of compounds (–)-**12** and **22** (1:1, 0.105 mg, total yields 7.2%).

4.4.1. (–)-6-Hydroxymethylimonene [((1*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)methanol] (–)-12**.** The NMR spectra of compound (–)-**12** was recorded for its mixture with compound **22** in the ratio (–)-**12**/**22** = 5:1. ¹H NMR (CDCl₃, 400 MHz): δ 5.54–5.49 (1H, m, H₂), 4.69 (2H, s, H₉), 3.70 (1H, dd, ²J = 10.7 Hz, J_{11',6} = 3.5 Hz, H_{11'}), 3.55 (1H, dd, ²J = 10.7 Hz, J_{11,6} = 8.6 Hz, H₁₁), 2.29–2.12 (2H, m, H₄, H₆), 2.11–2.01 (1H, m, H_{3'}), 1.95–1.88 (1H, m, H_{5'}), 1.88–1.78 (1H, m, H₃), 1.70 (3H, s, Me₁₀), 1.70–1.67 (3H, m, Me₇), 1.56–1.47 (1H, m, H₅). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 149.6 (s, C₈), 132.3 (s, C₁), 124.3 (d, C₂), 108.5 (t, C₉), 64.0 (t, C₁₁), 42.1 (d, C₆), 36.0 (d, C₄), 30.7 (t, C₃), 29.5 (t, C₅), 22.0 (q, C₇), 20.7 (q, C₁₀).

4.4.2. (S)-(2-Methyl-5-(propan-2-ylidene)cyclohex-2-en-1-yl)-methanol **22.** The NMR spectra of compound **22** was recorded for its mixture with compound (–)-**12** in the ratio (–)-**12**/**22** = 0.7:1. ¹H NMR (CDCl₃, 400 MHz): δ 5.48–5.41 (1H, m, H₂), 3.60 (1H, dd, ²J = 10.4 Hz, J_{11',6} = 3.3 Hz, H_{11'}), 3.41 (1H, dd, ²J = 10.4 Hz, J_{11,6} = 7.6 Hz, H₁₁), 2.80 (1H, dm, ²J = 19.8 Hz, H_{3'}), 2.71 (1H, dd, ²J = 13.5 Hz, J_{5',6} = 3.1 Hz, H_{5'}), 2.58 (1H, dm, ²J = 19.8 Hz, H₃), 2.25–2.11 (1H, m, H₆), 2.15–2.05 (1H, m, H₅), 1.70 and 1.68 (6H, 2s, Me₇, Me₁₀), 1.62 (3H, s, Me₉). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 133.3 (s, C₁), 125.4 (s, C₄), 123.7 (s, C₈), 123.5 (d, C₂), 64.2 (t, C₁₁), 43.5 (d, C₆), 29.6 (t, C₃), 29.2 (t, C₅), 21.9 (q, C₇), 20.0 (q, C₉), 19.7 (q, C₁₀).

4.4.3. Reaction of Compounds (–)-12** and **22** Mixtures with Salicylic Aldehyde **10a**.**

- Without solvent: To suspension of montmorillonite K10 (0.100 g) in 1 mL of CH₂Cl₂ a solution of salicylic aldehyde **10a** (0.050 g, 0.41 mmol) and (–)-**12** and **22** mixture (0.050 g) in 1 mL of CH₂Cl₂ was added. The solvent was distilled off. The reaction mixture was kept at room temperature for 1 h. Ethyl acetate was added, and the clay was filtered. The resulting solution was analyzed by GC–MS (see Table 1).
- In the presence of solvent: To suspension of montmorillonite K10 (0.100 g) in 1 mL of CH₂Cl₂ a solution of salicylic aldehyde **10a** (0.050 g, 0.41 mmol) and (–)-**12** and **22** mixture (0.050 g) in 1 mL of CH₂Cl₂ was added. The reaction mixture was stirred at room temperature for 1 h. Ethyl acetate was added, and the clay was filtered. The resulting solution was analyzed by GC–MS (see Table 1).

4.4.4. Reaction of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17** and 2,4-Dihydroxybenzaldehyde **10b**.** According to GP, reaction of 2,4-dihydroxybenzaldehyde **10b** (0.25 g, 1.8 mmol, 1 equiv), acetate (–)-**17** (0.40 g, 1.8 mmol, 1 equiv) in the presence of K10 (2.0 g) gave compounds (–)-**13** (0.047 g, 16%) and (+)-**19c** (0.217 g, 43%).

4.4.5. (3*S*,6*aR*,12*bR*)-4,7,7-Trimethyl-3,6-dihydro-2*H*,7*H*,12*bH*-3,6*a*-methanooxocino[3,2-*c*]chromen-10-ol (–)-19b**.** A white waxy compound; [α]_D²⁵ +68 (c 0.2, CHCl₃). ¹H NMR (CDCl₃, 600 MHz): δ 7.23 (1H, dd, J_{15,14} = 8.4 Hz, J_{15,14} = 0.8 Hz, H₁₅), 6.37 (1H, dd, J_{14,15} = 8.4 Hz, J_{14,12} = 2.5 Hz, H₁₄), 6.23 (1H, d, J_{12,14} = 2.5 Hz, H₁₂), 5.50–5.47 (1H, m, H₅), 4.40 (1H, s, H₁), 3.83 (1H, dd, ²J = 10.9 Hz, J_{2',3} = 1.8 Hz, H_{2'}), 3.73 (1H, dd, ²J = 10.9 Hz, J_{2,3} = 2.1 Hz, H₂), 2.26 (1H, dm, ²J = 19.1 Hz, H_{6'}), 2.12–2.09 (1H, m, H₃), 1.84 (1H, dm, ²J = 19.1 Hz, H₆), 1.73 (1H, dm, ²J = 11.6 Hz, H_{8'}), 1.71–1.69 (3H, m, Me₁₆), 1.61 (1H, dd, ²J = 11.6 Hz, J_{8,3} = 3.2 Hz, H₈), 1.30 (3H, s, Me₁₈), 1.26 (3H, s, Me₁₇). ¹³C{¹H} NMR (CDCl₃, 151 MHz): δ 156.0 (s, C₁₃), 153.7 (s, C₁₁), 134.1 (s, C₄), 127.9 (d, C₁₅), 123.6 (d, C₅), 114.5 (s, C₁₀), 107.9 (d, C₁₄), 102.9 (d, C₁₂), 81.2 (s, C₉), 78.7 (d, C₁), 69.3 (t, C₂), 36.8 (d, C₃), 35.4 (s, C₇), 31.2 (t, C₈), 27.4 (t, C₆), 23.1 (q, C₁₈), 22.2 (q, C₁₇), 21.7 (q, C₁₆). HRMS *m/z*: [M]⁺ calcd for C₁₈H₂₂O, 286.1564; found, 286.1560.

4.4.6. Reaction of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17** and 2-Hydroxy-3-methoxybenzaldehyde **10c**.** According to GP, reaction of 2-hydroxy-3-methoxybenzaldehyde **10c** (1.00 g, 6.6 mmol, 1 equiv), acetate (–)-**17** (1.50 g, 6.6 mmol, 1 equiv) in the presence of K10 (7.5 g) gave compounds (+)-**7c** (0.139 g, 7%), (–)-**13** (0.230 g, 10%), (–)-**14c** (0.123 g, 6%), (+)-**19c** (0.427 g, 21%) and

mixture of compounds (–)-**20c** and (–)-**21c** (0.315 g, (–)-**21c**/(–)-**20c** = 2.0, 15%). Compound (–)-**21c** was isolated in individual form by further CC on SiO₂.

4.4.7. (3*S*,6*aR*,12*bR*)-9-Methoxy-4,7,7-trimethyl-3,6-dihydro-2*H*,7*H*,12*bH*-3,6*a*-methanooxocino[3,2-*c*]chromen-10-ol (+)-19c**.** White powder; mp 84 °C with decomposition; [α]_D²⁵ +71 (c 0.2, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 7.03 (1H, dm, J_{15,14} = 7.9 Hz, H₁₅), 6.84 (1H, dd, J_{14,13} = J_{14,15} = 7.9 Hz, H₁₃), 6.76 (1H, dd, J_{13,14} = 8.1 Hz, J_{13,15} = 1.7 Hz, H₁₃), 5.50–5.45 (1H, m, H₅), 4.46 (s, 1H, H₁), 3.85 (1H, dm, ²J = 10.9 Hz, H_{2'}), 3.81 (3H, s, Me₁₉), 3.74 (1H, dd, ²J = 10.9 Hz, J_{2,3} = 2.1 Hz, H₂), 2.34 (1H, dm, ²J = 19.1 Hz, H_{6'}), 2.13–2.08 (1H, m, H₃), 1.85 (1H, dm, ²J = 19.0 Hz, H₆), 1.76 (1H, dm, ²J = 11.7 Hz, H_{8'}), 1.72–1.67 (3H, m, Me₁₆), 1.62 (1H, dd, ²J = 11.6 Hz, J_{8,3} = 3.2 Hz, H₈), 1.40 (3H, s, Me₁₈), 1.30 (3H, s, Me₁₇). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 147.8 (s, C₁₂), 142.0 (s, C₁₁), 133.9 (s, C₄), 123.5 (d, C₅), 122.5 (s, C₁₀), 119.7 (d, C₁₄), 118.6 (d, C₁₅), 110.5 (d, C₁₃), 81.2 (s, C₉), 78.6 (d, C₁), 69.4 (t, C₂), 55.8 (q, C₁₉), 36.7 (d, C₃), 35.0 (s, C₇), 31.1 (t, C₈), 27.5 (t, C₆), 23.0 (q, C₁₈), 22.0 (q, C₁₇), 21.6 (q, C₁₆). HRMS *m/z*: [M]⁺ calcd for C₁₉H₂₄O₃, 300.1720; found, 300.1718.

4.4.8. 2-Methoxy-6-((3*S*,4*aS*,5*S*,8*R*,8*aR*)-2,2,8*a*-trimethylhexahydro-2*H*,5*H*-3,8-methanopyrano[4,3-*b*]pyran-5-yl)phenol (–)-21c**.** White powder; mp 130.0 °C with decomposition; [α]_D²⁴ –59 (c 0.4, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ 6.89 (1H, dd, J_{19,18} = 7.6 Hz, J_{19,17} = 1.7 Hz, H₁₉), 6.80 (1H, dd, J_{18,17} = 8.0 Hz, J_{18,19} = 7.6 Hz, H₁₈), 6.77 (1H, s, OH), 6.75 (1H, dd, J_{17,18} = 8.0 Hz, J_{17,19} = 1.8 Hz, H₁₇), 3.85 (3H, s, Me₂₀), 4.89 (1H, s, H₂), 3.80 (1H, dd, ²J = 11.4 Hz, J_{4',5} = 1.6 Hz, H_{4'}), 3.72 (1H, dd, ²J = 11.4 Hz, J_{4,5} = 2.0 Hz, H₄), 2.29–2.16 (1H, m, H_{6'}), 2.15 (1H, dm, J_{1,8} = 11.1 Hz, H₁), 1.73 (1H, dm, J_{5,6'} = 11.2 Hz, H₅), 1.68–1.50 (3H, m, H₆, 2H₈), 1.50–1.44 (1H, m, H₇), 1.35 (3H, s, Me₁₀), 1.22 (3H, s, Me₁₃), 1.16 (3H, s, Me₁₂). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 146.5 (s, C₁₆), 142.8 (s, C₁₅), 125.7 (s, C₁₄), 118.83 and 118.77 (2d, C₁₈, C₁₉), 109.3 (d, C₁₇), 75.8 (d, C₂), 72.1 (s, C₁₁), 70.7 (s, C₉), 70.4 (t, C₄), 55.8 (q, C₂₀), 40.2 (d, C₁), 36.6 (d, C₅), 33.3 (d, C₇), 28.8 and 28.7 (2q, C₁₂, C₁₃), 27.2 (t, C₆), 22.9 (t, C₈), 22.8 (q, C₁₀). HRMS *m/z*: [M]⁺ calcd for C₁₉H₂₆O₄, 318.1826; found, 318.1830.

4.4.9. 2-((2*R*,3*aS*,4*S*,7*R*,7*aR*)-2-Isopropyl-7*a*-methylhexahydro-4*H*-2,7-methanofuro[3,2-*c*]pyran-4-yl)-6-methoxyphenol (–)-20c**.** The NMR spectra of compound (–)-**20c** was recorded for its mixture with compound (–)-**21c** in the ratio (–)-**20c**/(–)-**21c** = 3:1. ¹H NMR (CDCl₃, 400 MHz): δ 6.89 (1H, dd, J_{19,18} = 7.8 Hz, J_{19,17} = 1.5 Hz, H₁₉), 6.82 (1H, dd, J_{18,17} = 8.0 Hz, J_{18,19} = 7.8 Hz, H₁₈), 6.76 (1H, dd, J_{17,18} = 8.0 Hz, J_{17,19} = 1.7 Hz, H₁₇), 6.67 (1H, s, OH), 4.67 (1H, d, J_{2,1} = 1.7 Hz, H₂), 4.06 (1H, br.d, ²J = 11.9 Hz, H_{4'}), 3.62 (1H, dd, ²J = 11.9 Hz, J_{4,5} = 1.5 Hz, H₄), 2.31–2.23 (1H, m, H₁), 1.97 (1H, sept, J_{11,12} = J_{11,13} = 6.9 Hz, H₁₁), 1.91–1.81 (2H, m, H₅, H_{6'}), 1.66–1.62 (1H, m, H₆), 1.57–1.43 (2H, m, 2H₈), 1.50 (3H, s, Me₁₀), 0.90 and 0.88 (6H, 2d, J_{12,11} = J_{13,11} = 6.9 Hz, Me₁₂, Me₁₃). ¹³C{¹H} NMR (CDCl₃, 100 MHz): δ 146.6 (s, C₁₆), 142.6 (d, C₁₅), 126.7 (s, C₁₄), 119.2 (d, C₁₈), 118.2 (d, C₁₉), 109.4 (d, C₁₇), 88.2 (s, C₇), 81.0 (s, C₉), 74.0 (d, C₂), 67.4 (t, C₄), 55.8 (q, C₂₀), 46.8 (d, C₁), 42.9 (d, C₅), 37.7 (t, C₆), 33.5 (t, C₈), 32.8 (d, C₁₁), 18.1 (q, C₁₀), 18.0 and 17.9 (2q, C₁₂, C₁₃). HRMS *m/z*: [M]⁺ calcd for C₁₉H₂₆O₄, 318.1826; found, 318.1832.

4.4.10. (2*aS*,2*a'*¹*S*,5*aR*,10*bS*)-4-Isopropyl-7-methoxy-2*a'*¹-methyl-2,2*a*,2*a'*¹,3,5*a*,10*b*-hexahydrofuro[4,3,2-*k'*]xanthene (+)-7c**.** Colorless oil; [α]_D²⁶ +10 (c 0.5, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ 6.94–6.88 (2H, m, H₁₉, H₂₀), 6.84 (1H, dd, J_{18,19} = 7.1 Hz, J_{18,20} = 2.5 Hz, H₁₈), 5.67–5.64 (1H, m, H₁₁), 4.47 (1H, s, H₅), 4.07–4.02 (1H, m, H₁), 3.96 (1H, dd, ²J = J_{7,8} = 7.9 Hz, H_{7'}), 3.84 (3H, s, Me₂₁), 3.66 (1H, dd, ²J = 7.9 Hz, J_{7,8} = 9.0 Hz, H₇), 2.49–2.41 (1H, m, H₈), 2.26 (1H, sept, J_{13,14} = J_{13,15} = 6.9 Hz, H₁₃), 2.25–2.16 (1H, m, H_{9'}), 2.12 (1H, dd, ²J = 17.2 Hz, J_{9,8} = 2.7 Hz, H₉), 1.13 (3H, s, Me₁₆), 1.01 (3H, d, J_{15,13} = 6.9 Hz, Me₁₅), 1.00 (3H, d, J_{14,13} = 6.9 Hz, Me₁₄). ¹³C{¹H} NMR (CDCl₃, 125.77 MHz): δ 148.8 (s, C₁₇), 146.1 (s, C₁₀), 144.8 (s, C₃), 127.4 (s, C₄), 121.5 (d, C₁₉), 121.3 (d, C₂₀), 117.2 (d, C₁₁), 111.7 (d, C₁₈), 82.7 (d, C₅), 78.3 (d, C₁), 73.1 (t, C₇), 55.8 (q, C₂₁), 46.2 (s, C₁₂), 44.4 (d, C₈), 34.6 (d, C₁₃), 24.5 (t, C₉), 23.6 (q, C₁₆), 20.7 and 20.6 (2q, C₁₄, C₁₅). HR-MS: 300.1722 (M⁺, C₁₉H₂₄O₃);

calcd. 300.1720). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1722.

4.4.11. *2-((1S,4S,4aR,7S,8aR)-4a,6-Dimethyl-3,4,4a,7,8,8a-hexahydro-1H-4,7-methanoisochromen-1-yl)-6-methoxyphenol (–)-14c*. Colorless oil; $[\alpha]_D^{25}$ –55 (c 0.3, $CHCl_3$). 1H NMR ($CDCl_3$, 300 MHz): δ 7.44 (1H, s, OH), 6.78–6.70 (3H, m, H-17, H18, H19), 5.54–5.50 (1H, m, H9), 5.04 (1H, d, $J_{4,5}$ = 1.0 Hz, H4), 3.97 (1H, dd, 2J = 11.3 Hz, $J_{2,1}$ = 1.5 Hz, H2'), 3.84 (3H, s, Me20), 3.76 (1H, dd, 2J = 11.3 Hz, $J_{2,1}$ = 1.8 Hz, H2), 2.24–2.16 (1H, m, H7), 1.75 (3H, d, $J_{12,9}$ = 1.6 Hz, Me12), 1.72–1.64 (1H, m, H5), 1.64–1.56 (2H, m, 2H11), 1.59–1.52 (1H, m, H6_{en}), 1.36 (3H, s, Me13), 1.31–1.22 (1H, m, H1), 1.19–1.08 (1H, m, H6_{ex}). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 147.1 (s, C16), 145.5 (s, C8), 143.8 (s, C15), 131.6 (d, C9), 126.7 (s, C14), 118.8 (d, C18), 118.6 (d, C19), 109.4 (d, C17), 74.4 (d, C4), 67.8 (t, C2), 55.8 (q, C20), 40.8 (d, C5), 36.3 (d, C1), 35.1 (d, C7), 34.8 (s, C10), 32.6 (t, C11), 28.3 (t, C6), 20.7 (q, C13), 19.5 (q, C12). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1715.

4.4.12. *Reaction of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17 and 2-Hydroxy-5-methoxybenzaldehyde 10d*. According to GP, reaction of 2-hydroxy-5-methoxybenzaldehyde **10d** (0.67 g, 6.6 mmol, 1 equiv), acetate (–)-17 (1.00 g, 6.6 mmol, 1 equiv) in the presence of K10 (5.0 g) gave compounds (+)-7c (0.074 g, 6%), (–)-13 (0.185 g, 25%), (–)-14d (0.124 g, 9%), (+)-19d (0.344 g, 26%) and mixture of compounds (–)-20d and (–)-21d (0.195 g, (–)-21d/(–)-20d = 1.5, 14%). Compound (–)-21d was isolated in individual form by further CC on SiO_2 .

4.4.13. *(3S,6aR,12bR)-11-Methoxy-4,7,7-trimethyl-3,6-dihydro-2H,7H,12bH-3,6a-methanooxocino[3,2-c]chromen (+)-19d*. White powder; mp 117.7 °C with decomposition; $[\alpha]_D^{26}$ +80 (c 0.3, $CHCl_3$). 1H NMR ($CDCl_3$, 600 MHz): δ 6.72 (1H, dd, $J_{13,12}$ = 8.9 Hz, $J_{12,15}$ = 3.1 Hz, H13), 6.95 (1H, d, $J_{15,12}$ = 3.1 Hz, H15), 6.67 (1H, d, $J_{12,13}$ = 8.9 Hz, H12), 5.52–5.48 (1H, m, H5), 4.42 (1H, s, H1), 3.86 (1H, dm, 2J = 10.9 Hz, H2'), 3.75 (1H, dd, 2J = 10.9 Hz, $J_{2,3}$ = 2.2 Hz, H2), 3.73 (3H, s, Me19), 2.30 (1H, dm, 2J = 19.1 Hz, H6'), 2.10–2.13 (1H, m, H3), 1.84 (1H, dm, 2J = 19.1 Hz, H6), 1.74 (1H, dm, 2J = 11.6 Hz, H8'), 1.73–1.70 (3H, m, Me16), 1.62 (1H, dd, 2J = 11.6 Hz, $J_{8,3}$ = 3.2 Hz, H8), 1.30 (3H, s, Me18), 1.24 (3H, s, Me17). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 153.5 (s, C14), 146.4 (s, C11), 134.1 (s, C4), 123.7 (d, C5), 122.1 (s, C10), 117.1 (d, C12), 115.6 (d, C13), 110.6 (d, C15), 80.4 (s, C-9), 78.9 (d, C1), 69.5 (t, C2), 55.5 (q, C19), 36.8 (d, C3), 35.3 (s, C7), 31.2 (t, C8), 27.6 (t, C6), 23.1 (q, C18), 22.0 (q, C17), 21.7 (q, C16). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1716.

4.4.14. *4-Methoxy-2-((3S,4aS,5S,8R,8aR)-2,2,8a-trimethylhexahydro-2H,5H-3,8-methanopyrano[4,3-b]pyran-5-yl)phenol (–)-21d*. White powder; mp 119.8–122.4 °C; $[\alpha]_D^{26}$ –61 (c 0.2, $CHCl_3$). 1H NMR ($CDCl_3$, 500 MHz): δ 8.17 (1H, s, OH), 6.75 (1H, d, $J_{16,17}$ = 8.8 Hz, H16), 6.69 (1H, dd, $J_{17,16}$ = 8.8 Hz, $J_{17,19}$ = 3.0 Hz, H17), 6.46 (1H, d, $J_{19,17}$ = 3.0 Hz, H19), 4.85 (1H, s, H2), 3.81 (1H, d, 2J = 11.2 Hz, H4'), 3.74 (1H, d, 2J = 11.2 Hz, H4), 3.72 (3H, s, Me20), 2.29–2.21 (1H, m, H6'), 2.13–2.07 (1H, m, H1), 1.99–1.88 (1H, m, H8'), 1.81–1.74 (1H, m, H5), 1.59–1.48 (3H, m, H6, H7, H8), 1.31 (3H, s, Me10), 1.24 (3H, s, Me13), 1.20 (3H, s, Me12). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.77 MHz): δ 152.5 (s, C18), 150.2 (s, C15), 123.7 (s, C14), 117.5 (d, C16), 113.3 (d, C17), 112.0 (d, C19), 80.3 (d, C2), 72.3 (s, C11), 70.5 (t, C4), 70.2 (s, C9), 55.6 (q, C20), 41.6 (d, C1), 36.3 (d, C5), 33.1 (d, C7), 28.8 and 28.7 (2q, C12, C13), 27.0 (t, C6), 23.7 (t, C8), 22.9 (q, C10). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{26}O_4$, 318.1826; found, 318.1822.

4.4.15. *2-((2R,3aS,4S,7R,7aR)-2-Isopropyl-7a-methylhexahydro-4H-2,7-methanofuro[3,2-c]pyran-4-yl)-6-methoxyphenol (–)-20d*. The NMR spectra of compound (–)-20d was recorded for its mixture with compound (–)-21d in the ratio (–)-20d/(–)-21d = 1:1.3.

1H NMR ($CDCl_3$, 400 MHz): δ 8.22 (1H, s, OH), 6.77 (1H, d, $J_{16,17}$ = 8.8 Hz, H16), 6.72–6.68 (1H, m, H17), 6.47 (1H, d, $J_{19,17}$ = 3.0 Hz, H19), 4.62 (1H, d, $J_{2,1}$ = 1.6 Hz, H2), 4.09 (1H, br.d, 2J = 11.9 Hz, H4'), 3.72 (3H, s, Me20), 3.64 (1H, dd, 2J = 11.9 Hz, $J_{4,5}$ = 1.4 Hz, H4), 2.30–2.20 (1H, m, H1), 2.01–1.81 (3H, m, H5, H6', H11), 1.73–1.65 (1H, m, H8'), 1.64–1.55 (2H, m, H6, H8), 1.48 (3H, s, Me10), 0.92 and 0.91 (6H, 2d, $J_{12,11}$ = $J_{13,11}$ = 6.8 Hz, Me12, Me13). NMR $^{13}C\{^1H\}$

NMR ($CDCl_3$, 100 MHz): δ 152.7 (s, C18), 149.7 (s, C15), 124.9 (s, C14), 117.5 (d, C16), 113.5 (d, C17), 112.1 (d, C19), 88.4 (s, C7), 80.7 (s, C9), 77.9 (d, C2), 67.4 (t, C4), 55.7 (q, C20), 47.5 (d, C1), 42.6 (d, C5), 37.3 (t, C6), 34.3 (t, C8), 32.7 (d, C11), 18.1 (q, C10), 18.0 and 17.9 (2q, C12, C13). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{26}O_4$, 318.1826; found, 318.1830.

4.4.16. *(2aS,2a'S,5aR,10bS)-4-Isopropyl-9-methoxy-2a'-methyl-2,2a,2a',3,5a,10b-hexahydrofuro[4,3,2-kl]xanthene (+)-7d*. Colorless oil; $[\alpha]_D^{25}$ +30 (c 0.3, $CHCl_3$). 1H NMR ($CDCl_3$, 600 MHz): δ 6.83 (1H, d, $J_{20,18}$ = 3.0 Hz, H20), 6.76 (1H, dd, $J_{17,18}$ = 8.7 Hz, H-17), 6.76 (1H, dd, $J_{18,17}$ = 8.7 Hz, $J_{18,20}$ = 3.0 Hz, H18), 5.60–5.63 (1H, m, H11), 4.46 (1H, s, H5), 3.96 (1H, dd, 2J = $J_{7,8}$ = 7.8 Hz, H7'), 3.91 (1H, br.d, $J_{1,11}$ = 4.5 Hz, H1), 3.74 (3H, s, Me21), 3.65 (1H, dd, 2J = 7.8 Hz, $J_{7,8}$ = 9.5 Hz, H7), 2.47–2.40 (1H, m, H8), 2.28 (1H, sept, $J_{13,14}$ = $J_{13,15}$ = 6.8 Hz, H13), 2.26–2.17 (1H, m, H9'), 2.12 (1H, dd, 2J = 17.3 Hz, $J_{9,8}$ = 2.9 Hz, H9), 1.11 (3H, s, Me16), 1.025 (3H, d, $J_{15,13}$ = 6.8 Hz, Me15), 1.022 (3H, d, $J_{14,13}$ = 6.8 Hz, Me14). NMR $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150.9 MHz): δ 154.3 (s, C19), 150.1 (s, C3), 146.3 (s, C10), 127.5 (s, C4), 118.0 (d, C17), 116.7 (d, C11), 114.8 (d, C18), 114.1 (d, C20), 83.4 (d, C5), 78.2 (d, C1), 73.0 (t, C7), 55.4 (q, C21), 46.1 (s, C12), 44.3 (d, C8), 34.6 (d, C13), 24.2 (t, C9), 23.7 (q, C16), 20.8 and 20.6 (2q, C14, C15). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1718.

4.4.17. *2-((1S,4S,4aR,7S,8aR)-4a,6-Dimethyl-3,4,4a,7,8,8a-hexahydro-1H-4,7-methanoisochromen-1-yl)-4-methoxyphenol (–)-14d*. Colorless oil; $[\alpha]_D^{26}$ –57 (c 0.4, $CHCl_3$). 1H NMR ($CDCl_3$, 400 MHz): δ 8.49 (1H, s, OH), 6.75 (1H, d, $J_{16,17}$ = 8.8 Hz, H16), 6.69 (1H, dd, $J_{17,16}$ = 8.8 Hz, $J_{17,19}$ = 2.8 Hz, H17), 6.37 (1H, d, $J_{19,17}$ = 2.8 Hz, H19), 5.56–5.50 (1H, m, H9), 4.99 (1H, d, $J_{4,5}$ = 1.8 Hz, H4), 3.97 (1H, dd, 2J = 11.4 Hz, $J_{2,1}$ = 1.4 Hz, H2'), 3.69 (3H, s, Me20), 3.77 (1H, dd, 2J = 11.4 Hz, $J_{2,1}$ = 1.6 Hz, H2), 2.27–2.20 (1H, m, H7), 1.77 (3H, d, $J_{12,9}$ = 1.5 Hz, Me12), 1.70–1.50 (4H, m, H-5, H6_{en}, 2H11), 1.32 (3H, s, Me13), 1.40–1.30 (1H, m, H6_{ex}), 1.33–1.26 (1H, m, H1). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.4 (s, C18), 150.4 (s, C15), 145.7 (s, C8), 131.3 (d, C9), 125.1 (s, C14), 117.4 (d, C16), 113.4 (d, C17), 111.8 (d, C19), 77.5 (d, C4), 67.8 (t, C2), 55.6 (q, C20), 41.6 (d, C5), 36.0 (d, C1), 34.9 (d, C7), 34.5 (s, C10), 32.4 (t, C11), 28.9 (t, C6), 20.8 (q, C13), 19.5 (q, C12). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1718.

4.4.18. *Reaction of (–)-8-Acetoxy-6-hydroxymethylimonene (–)-17 and 2-Hydroxy-4-methoxybenzaldehyde 10e*. According to GP, reaction of 2-hydroxy-4-methoxybenzaldehyde **10e**, synthesized according,⁵⁵ (0.42 g, 2.8 mmol, 1 equiv), acetate (–)-17 (0.63 g, 2.8 mmol, 1 equiv) in the presence of K10 (3.16 g) gave compounds (–)-13 (0.076 g, 16%) and (+)-19e (0.260 g, 31%).

4.4.19. *(3S,6aR,12bR)-10-Methoxy-4,7,7-trimethyl-3,6-dihydro-2H,7H,12bH-3,6a-methanooxocino[3,2-c]chromen (+)-19e*. Colorless oil; $[\alpha]_D^{26}$ +61 (c 0.2, $CHCl_3$). 1H NMR ($CDCl_3$, 600 MHz): δ 7.28 (1H, dd, $J_{15,14}$ = 8.6 Hz, $J_{15,14}$ = 1.0 Hz, H15), 6.48 (1H, dd, $J_{14,15}$ = 8.6 Hz, $J_{14,12}$ = 2.6 Hz, H14), 6.30 (1H, d, $J_{12,14}$ = 2.6 Hz, H12), 5.50–5.46 (1H, m, H5), 4.41 (1H, s, H1), 3.84 (1H, dm, 2J = 10.9 Hz, H2'), 3.74 (1H, dd, 2J = 10.9 Hz, $J_{2,3}$ = 2.1 Hz, H2), 3.73 (3H, s, Me19), 2.28 (1H, dm, 2J = 19.1 Hz, H6'), 2.13–2.09 (1H, m, H3), 1.83 (1H, dm, 2J = 19.1 Hz, H6), 1.74 (1H, dm, 2J = 11.6 Hz, H8'), 1.68–1.72 (3H, m, Me16), 1.62 (1H, dd, 2J = 11.6 Hz, $J_{8,3}$ = 3.2 Hz, H8), 1.31 (3H, s, Me18), 1.27 (3H, s, Me17). NMR $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 160.0 (s, C13), 153.5 (s, C11), 134.2 (s, C4), 127.6 (d, C15), 123.6 (d, C5), 114.3 (s, C10), 107.2 (d, C14), 100.9 (d, C12), 81.2 (s, C9), 78.7 (d, C1), 69.3 (t, C2), 55.1 (q, C19), 36.8 (d, C3), 35.4 (s, C7), 31.1 (t, C8), 27.4 (t, C6), 23.1 (q, C18), 22.2 (q, C17), 21.7 (q, C16). HRMS m/z : $[M]^+$ calcd for $C_{19}H_{24}O_3$, 300.1720; found, 300.1723.

4.5. X-ray Diffraction Data. The X-ray diffraction data were collected with a Bruker KAPPA APEX II CCD diffractometer with graphite monochromated Mo $K\alpha$ radiation (0.71073 Å) at the Collective Chemical Service Center of Siberian Branch of the Russian Academy of Sciences. Absorption corrections were applied with Siemens Area Detector Absorption Correction Software (SADABS). The structure was solved by the direct method. The positions and temperature factors for the non-hydrogen atoms were refined

anisotropically by the full-matrix least-squares technique. All computations were done with the SHELX-2018/3 program suite.

Crystal data and structure refinement for (+)-**19d** and (–)-**21a** see Figure 3 and Table S2. Deposition numbers 2353259 (for (+)-**19d**) and 2353260 (for (–)-**21a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

4.6. Computational Methods. Low energy conformers were located with the ETKDGV3 algorithm⁵⁶ implemented in RDKit v. 2022.09.5 and optimized using XTb then with Gaussian 16 (G16, Revision C.01).⁵⁷ Single point energies were performed at the PBE0/D3BJ level in combination with the def2-TZVP basis set.⁵⁸ All structures were fully optimized with G16 at the M06-2X/6-31+G(d,p)/UF level of theory with Grimmes dispersion correction included. The implicit SMD solvation model was used to simulate dichloromethane. Harmonic frequencies were used to verify geometry minima. All calculations are reported in kcal/mol.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.4c01282>.

Table (composition of acetate (–)-**17** and salicylaldehyde reaction products on different catalysts), Scheme (formation of additional possible products from (–)-**12** and **22**), Cartesian coordinates for optimized structures, spectral data including 1D (¹H, ¹³C{¹H}NMR), and 2D NMR experiments (HSQC, HMBC, COSY, NOESY), HR-MS and X-ray diffraction analysis ([PDF](#))

Accession Codes

CCDC 2353259 for (+)-**19d** and CCDC 2353260 for (–)-**21a** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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