Tropane Skeleta from the Intramolecular Photocycloaddition of (4+3) Cycloadducts of Oxidopyridinium Ions and Dienes

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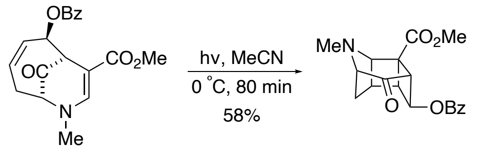
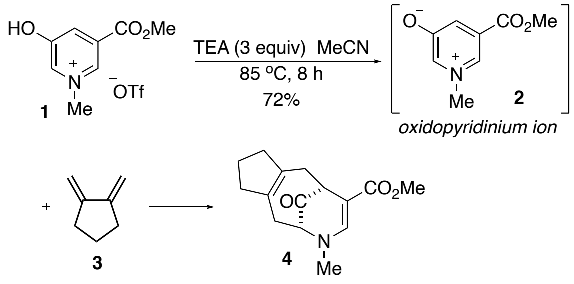
Supporting Information Placeholder



ABSTRACT: Easily prepared cycloadducts derived from the (4+3)-cycloaddition of oxidopyridinium ions with dienes reacted intramolecularly in a [2+2] cycloaddition process to afford complex polycyclic species in which the tropane skeleton was embedded.

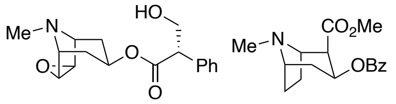
We have been investigating the intermolecular (4+3) cycloaddition reaction[1] of selected oxidopyridinium ions with dienes and have reported that the process is generally quite effective in terms of yield.[2] Complete control of regioselectivity and *endo*/*exo* selectivity remain to be fully optimized, though progress has been made on both fronts.[2,3] An example is shown in Scheme 1. As part of that program, the chemistry of the cycloadducts has become of interest. We realized that the cycloadducts were primed for an intramolecular [2+2] photochemical cycloaddition, which would lead to molecularly complex scaffolds in which the tropane skeleton is embedded. This letter reports our successful realization of this process.

SCHEME 1. Endo Selective (4+3)-Cycloaddition of an Oxidopyridinium Ion



Cycloadducts such as **4** possess both a simple, substituted alkene as well as a vinylogous carbamate. Some photochemistry of vinylogous carbamates and amides has been reported.[4] We thus expected the cycloadducts we planned to examine to be excellent candidates for intramolecular cycloaddition, with a few exceptions (vide infra).

Tropane alkaloids have a long history in drug use and abuse.[5,6] Perhaps the two most "notorious" members of this class are scopolamine (**5**) and cocaine (**6**) (Figure 1). Both are characterized by an 8-azabicyclo[3.2.1]octane ring system and have notable biological activity. Scopolamine is an anticholinergic, muscarinic receptor antagonist used medicinally as an antinauseant and antispasmodic, with potential in the treatment of depression, and as a research tool to model neural degradation associated with diseases such as dementia (e.g., Alzheimer's).[7-9] While cocaine is used medically as a local anesthetic, it has greater renown as a drug of abuse.[5,10,11] However, the synthesis of tropane alkaloids remains of interest, for the treatment of cocaine addiction and as a tool for neuroscience.[12] We were motivated by the possibility of obtaining rigid molecular scaffolds that might be useful for functionalization in the design of biologically active molecules.



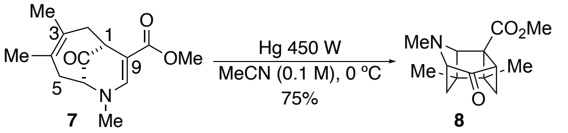
scopolamine (**5**) cocaine (**6**)

FIGURE 1. Examples of tropane alkaloids.

The precursors used in this study are the (4+3)-cycloadducts resulting from the reaction of dienes with the oxidopyridinium ion obtained from **1** upon treatment with base. Their syntheses have been reported elsewhere.[2,3]

When a solution of the (4+3)-cycloadduct **7** in acetonitrile in a borosilicate test tube was irradiated at a 0 ºC (bath) using a medium pressure mercury-vapor lamp, a new product was observed.[13] The reaction mixture was purified by flash chromatography to afford the pure product as a colorless oil in 75% yield (Scheme 2).[14] The ^1H spectrum of the isolated product revealed the disappearance of the downfield vinylic proton previously assigned to the vinylogous carbamate. The two methyl singlet peaks at 1.36 ppm and 1.19 ppm showed that the two vicinal methyl groups were still connected to tertiary carbons. The methyl singlet peak at 3.76 ppm in ^1H NMR, along with the peak at 171.1 ppm in ^{13}C NMR indicated the retention of the methyl ester. The data collectively suggested an intramolecular [2+2] cycloaddition between the alkene of the vinylogous carbamate and the alkene on the cycloheptanone ring, as we had expected.

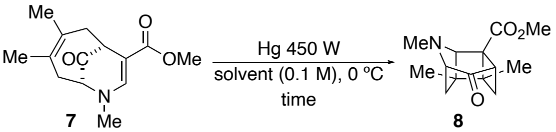
SCHEME 2. First Trial of Intramolecular Photocycloaddition



7 8

After obtaining [2+2]-cycloadduct in the photolysis trial, we set off to optimize the reaction conditions by examining the solvent effects and irradiation time on the reaction. The results are summarized in Table 1. Among all the solvents that were screened, chloroform was the only solvent that failed to yield the anticipated product, since the starting material decomposed relatively quicky under these reaction conditions (Table 1, entry 3). The best yield that was observed in the reaction of **7** was 96% when using acetonitrile as the solvent. We also observed a decrease of the product yield from 96% to 76% with additional irradiation for just half an hour, suggesting that the [2+2]-cycloadduct decomposed upon extended irradiation (Table 1, entries 7-8).

Table 1. Optimization of the Photolysis of 7



7 8

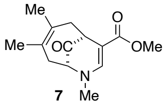
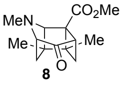
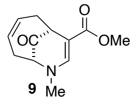
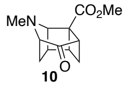
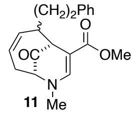
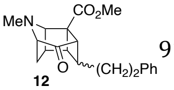
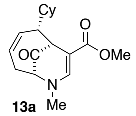
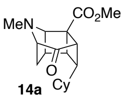
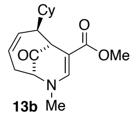
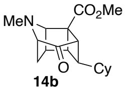
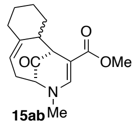
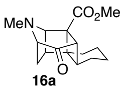
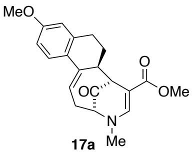
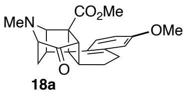
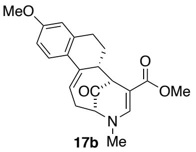
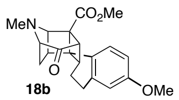
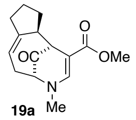
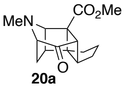
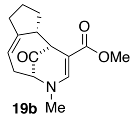
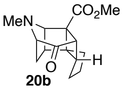
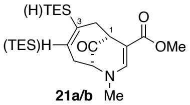
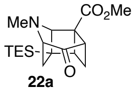
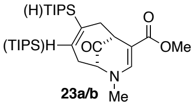
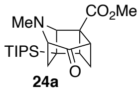
entry	solvent	time (h)	yield (%)[a]
1	toluene	2	90
2	CH$_2$Cl$_2$	2	84
3	CHCl$_3$	1.5	b
4	EtOAc	1.5	74
5	MeOH	1.5	66
6	MeCN	2	79
7	MeCN	2.5	96
8	MeCN	3	76

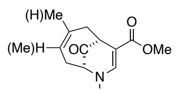
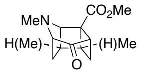
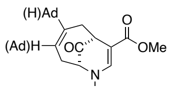
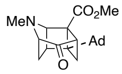
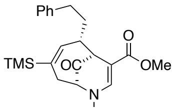
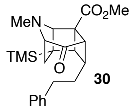
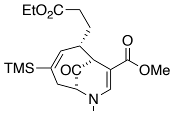
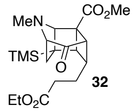
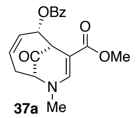
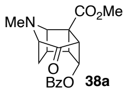
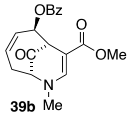
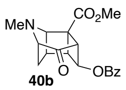
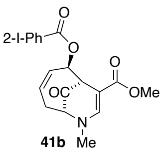
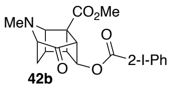
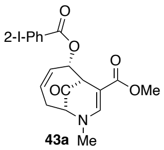
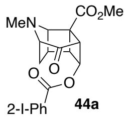
[a] Isolated yield after chromatographic purification. [b] Decomposition occurred.

With the data from Table 1 in hand, we proceeded to study the substrate scope of the reaction. The results are summarized in Table 2. In general, the reactions were conducted in acetonitrile at 0 ºC with irradiation times ranging from 1.3 to 2.5 h.

The parent system **9** underwent cycloaddition uneventfully and in high yield (Table 2, entry 2). Substitution at the 2 position was well tolerated regardless of stereochemistry, affording [2+2] cycloadducts in excellent yields (Table 2, entries 2-5). Fusing a ring between the 2 and 3 positions of the substrates led to an expected dichotomy in behavior. For example, the photocycloaddition of **15a** (from the mixture of **15a** and **15b**) proceeded to give **16a** in very good yield (Table 2, entry 6). Compound **15a** is *exo*,[3b] and produces a cycloadduct with a *cis*-fused six-membered ring. However, the *endo* isomer **15b** would be forced to pro-

Table 2. Intramolecular Photocycloadditions Producing Complex Tropanoids[a]

entry	substrate	time (h)	product	yield (%)
1	 7	2.5	 8	96
2	 9	2	 10	85
3	 11	0.5 (1)	 12	91 (79)[b]
4	 13a	2	 14a	76
5	 13b	2	 14b	75
6	 15ab	2.5	 16a	77[c-e]
7	 17a	2.5	 18a	59
8	 17b	2.5	 18b	0[e]
9	 19a	3	 20a	34
10	 19b	3	 20b	0[f]
11	 21a/b	2.5	 22a	37[g]
12	 23a/b	1.5	 24a	24[h]

13	 **25a/b**	5	 **26a/b**	75[i]
14	 **27a/b**	5	 **28a**	32[j]
15	 **29**	3	 **30**	0[k]
16	 **31**	2	 **32**	0[l]
17	 **37a**	1.5	 **38a**	60
18	 **39b**	1.3	 **40b**	58
19	 **41b**	2.5	 **42b**	62
20	 **43a**	2.5	 **44a**	54

[a] Reactions were conducted at 0 ºC in MeCN for the time indicated. [b] The starting material was a 46:54 mixture of *endo* and *exo* isomers, respectively. The product bore the same ratio by ^{1}H NMR. Data in parentheses shows that photolysis for a longer time leads to a lower yield. [c] The starting material was a 37:63 mixture of *endo* and *exo* isomers, respectively. [d] The yield is corrected based on starting material composition; the amount of the unreactive isomer was not included in the yield calculation. [e] A 22% yield of the *endo* starting material was recovered. [f] Only starting material was observed by TLC. It was not isolated after photolysis. [g] The starting material was a 59:41 mixture of 3-TES and 4-TES isomers as determined by NMR (See ref. 3b). [h] The starting material was a 54:46 mixture of 3-TES and 4-TES isomers as determined by NMR (See ref. 3b). [i] The starting material was a 55:45 mixture of regioisomers. The regioisomeric products were partially separable and could be characterized individually. See SI. [j] The starting material was a 50:50 mixture of regioisomers. [k] The starting material was an 81:13:6 mixture of isomers (See ref. 3b); the major isomer is shown. No evidence for any [2+2] cycloadduct was found. [l] The starting material was an 80:16:4 mixture of isomers (See ref. 3b); the major isomer is shown No evidence for any [2+2] cycloadduct was found.

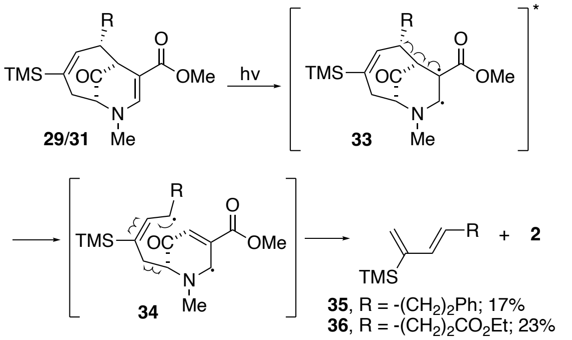
duce a *trans*-fused six-membered ring on the same cyclobutane unit and consequently **16b** is not formed (Table 2, entry 6). Other examples are in concert with this trend (Table 2, entries 7-10).

Interestingly, substitution of a trialkylsilyl group on the 4 position of the substrate seems to inhibit cycloaddition. Entries 11-12 of Table 2 show that when inseparable mixtures of 3 and 4 silylated substrates are photolyzed, only products derived from substrates with silyl substituents at the 4 position are isolated. The yields are low, but they represent yields calculated based on the entire mass of the starting substrate, including the isomer that does not produce a photocycloadduct. When a mixture of **25a**/**b** was photolyzed, both isomers produced a photocycloadduct. When a mixture of **27a/b (**Ad = 1-adamantyl) was similarly photolyzed, only cycloadduct **28a** was obtained. Its structure was confirmed by X-ray analysis. This compound possesses a regiochemistry opposite to that of **22b** and **24b**, suggesting that while sterics plays a role in the outcome of the photocycloaddition vis-à-vis the results from **25a/b**, there is likely another factor influencing and dominating the photocycloaddition of the silylated substrates. This observation warrants further investigation.

When the *endo* substrates **29** and **31** were photolyzed, no cycloadduct was formed. This is true not only for the major diastereomers shown in Table 2, but for minor, inseparable isomers that were part of the starting material Apparently, the combination of silyl substitution and substitution at position 4 combined to thwart the cycloaddition process. However, for both starting materials of these (4+3) cycloadducts, dienes **35** and **36** were produced in 17% and 23% yields, respectively. This represents a formal, photochemical retro-(4+3) cycloaddition, which we presently formulate as the result of two homolytic bond cleavages, as shown in Scheme 3.

Starting materials substituted at the 2 position with either a benzoyloxy or 2-iodobenzoyloxy group gave photocycloadducts in 54-62% yields, regardless of relative stereochemistry (Table 2, entries 17-20).

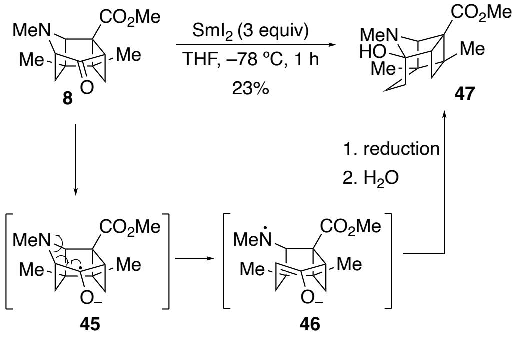
Scheme 3. Possible Mechanism for the Generation of Dienes 31 and 32



To demonstrate some chemistry of the photocycloadducts, we treated **8** with SmI_2. This resulted in the formation of **47** in 23% yield (not optimized, Scheme 4). Mechanistically, this result can be rationalized as an interrupted Clemmensen-Clemo-Prelog-Leonard reaction[15] in which the product **47** is unable to form an iminium ion and thus remains as the product.

In summary, we report that the intramolecular [2+2] photocycloadditions of 7-azabicyclo[4.3.1]deca-3,8-dien-10-ones, readily available products of the (4+3) cycloaddition of oxidopyridinium ions and dienes,[2,3] afford complex polycyclic structures containing the tropane ring system. The process promises to be applicable to many, but not all, such (4+3) cycloadducts, providing rapid access to rigid molecular scaffolds that could be of use in, *inter alia*, drug development. Further studies of the chemistry of the (4+3) cycloadducts are continuing. Results will be reported in due course.

Scheme 4. SmI_2 Reduction of Photocycloadduct 8.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, copies of NMR data, and X-ray data (PDF)

Accession Codes

CCDC 2133129- 2133131 and 2161820 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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REFERENCES

(1) (a) Harmata, M. The (4 + 3)-cycloaddition reaction: simple allylic cations as dienophiles. *Chem. Commun.* **2010**, *46*, 8886-8903. (b) Harmata, M. The (4 + 3)-cycloaddition reaction: heteroatom-substituted allylic cations as dienophiles. *Chem. Commun.* **2010**, *46*, 8904-8922. (c) Mascareñas, J. L.; Gulias, M.; Lopez, F. (4+3) cycloadditions. In *Cycloaddition Reactions in Organic Syntheses*, Nishiwaki, N., Ed.; John Wiley & Sons: Hoboken, 2014, pp 595-655. (d) Lam, S. Y. Y.; Chiu, P. [4+3] Cycloadditions of enol silane derivatives. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses,* Nishiwaki, N., Ed.; Wiley: New York, 2014; Chapter 18. (e) Jones, D. E.; Harmata, M. Application of the [4+3]-Cycloaddition Reaction to the Synthesis of Natural Products. In *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*; Nishiwaki, N., Ed.; Wiley: New York, 2014; Chapter 19. (f). Harmata, M. Fun with (4+3) cycloadditions. *Synlett* **2019**, *30*, 532–541.

(2) (a) Fu, C.; Lora, N.; Kirchhoefer, P. L.; Lee, D. R.; Altenhofer, E.; Barnes, C. L.; Hungerford, N. L.; Krenske, E. H.; Harmata, M., (4+3) Cycloaddition reactions of *N*-alkyl oxidopyridinium ions. *Angew. Chem., Int. Ed.* **2017**, *56*, 14682–14687. (b) Harmata, A. S.; Harmata, M., From 5-hydroxynicotinic acid to nitrogenous (4+3)-cycloadducts. *Org. Synth.* **2020**, *97*, 139–156.

(3) (a) Fu, C.; Kelley, S. P.; Tu, J.; Harmata, M., Generation of the 7-azabicyclo[4.3.1]decane ring system via (4 + 3) cycloaddition of oxidopyridinium ions. *J. Org. Chem.* **2021**, *86*, 7028-7037. (b) Sungnoi, W.; Keto, A. B.; Roseli, R. B.; Liu, J.; Wang, H.; Fu, C.; Regalado, E. L.; Krenske, E. H.; Harmata, M., Endo selectivity in the (4+3) cycloaddition of oxidopyridinium ions. *Org. Lett.* **2021,** *23*, 8302-8306

(4) For some examples, see: (a) Winkler, J. D.; Hershberger, P. M.; Springer, J. P., A stereoselective synthesis of the azaspiroundecane ring system of (-)-histrionicotoxin from (+)-glutamic acid. *Tetrahedron Lett.* **1986**, *27*, 5177-5180. (b) Winkler, J. D.; Hershberger, P. M., A stereoselective synthesis of (-)-perhydrohistrionicotoxin. *J. Am. Chem. Soc.* **1989**, *111*, 4852-4856. (c) Winkler, J. D.; Scott, R. D.; Williard, P. G., Asymmetric induction in the vinylogous amide photocycloaddition reaction. A formal synthesis of vindorosine. *J. Am. Chem. Soc.* **1990**, *112*, 8971-8975. (d) Comins, D. L.; Zheng, X., A novel approach to the perhydrohistrionicotoxin ring system. *J. Chem. Soc., Chem. Commun.* **1994**, 2681-2682. (e) Kwak, Y.-S.; Winkler, J. D., Synthesis of 6-aza-bicyclo[3,2,1]octan-3-ones via vinylogous imide photochemistry: An approach to the synthesis of the hetisine alkaloids. *J. Am. Chem. Soc.* **2001**, *123*, 7429-7430. (f) Ragains, J. R.; Winkler, J. D., Pseudosymmetry in azabicyclo[2.1.1]hexanes. A stereoselective construction of the bicyclic core of peduncularine. *Org. Lett.* **2006**, *8*, 4437-4440. (g) White, J. D.; Ihle, D. C., Tandem photocycloaddition-retro-Mannich fragmentation of enaminones. A route to spiropyrrolines and the tetracyclic Core of koumine. *Org. Lett.* **2006**, *8*, 1081-1084. (h) Sahn, J. J.; Comins, D. L., [2 + 2] Photochemical cycloaddition/ring opening of 6-alkenyl-2,3-dihydro-4-pyridones. *J. Org. Chem.* **2010**, *75*, 6728-6731.

(5) Drake, L. R.; Scott, P. J. H., DARK classics in chemical neuroscience: Cocaine. *ACS Chem. Neurosci.* **2018**, *9*, 2358-2372.

(6) Afewerki, S.; Wang, J. X.; Liao, W. W.; Córdova, A. In The Alkaloids: Chemistry and Biology; Knölker, H. J., Ed.; Elsevier: Cambridge, MA, 2019; Vol. 81, Chapter 3, pp 151–233.

(7) Ullrich, S. F.; Hagels, H.; Kayser, O., Scopolamine: a journey from the field to clinics. *Phytochem. Rev.* **2017**, *16*, 333-353.

(8) Drevets, W. C.; Bhattacharya, A.; Furey, M. L., The antidepressant efficacy of the muscarinic antagonist scopolamine: past findings and future directions. *Adv. Pharmacol.* **2020**, *89*, 357-386.

(9) Tang, K. S., The cellular and molecular processes associated with scopolamine-induced memory deficit: A model of Alzheimer's biomarkers. *Life Sci.* **2019,** *233*, 116695.

(10) Bezerra, M. M.; Leao, R. A. C.; Miranda, L. S. M.; de Souza, R. O. M. A., A brief history behind the most used local anesthetics. *Tetrahedron* **2020**, *76*, 131628.

(11) Brain, P. F.; Coward, G. A., A review of the history, actions, and legitimate uses of cocaine. *J. Subst. Abuse* **1989**, *1*, 431-451.

(12) Kohnen-Johannsen, K. L.; Kayser, O., Tropane alkaloids: chemistry, pharmacology, biosynthesis and production. *Molecules* **2019**, *24*, 796/1.

(13) We conducted the photolysis at 0 ºC to mitigate against any untoward effects of the heat generated by the lamp.

(14) Repeated sampling for TLC analysis may have lowered the yield.

(15). For examples and leading references, see: Zhang, J.; Wang, Y.-Q.; Wang, X.-W.; Li, W.-D. Z., Transannular reductive rearrangement of α-amino ketones: Construction of aza-tricyclic frameworks of several alkaloids. *J. Org. Chem.* **2013,** *78*, 6154-6162.