Ring expansion, ring contraction, and annulation reactions of allylic phosphonates under oxidative cleavage conditions.

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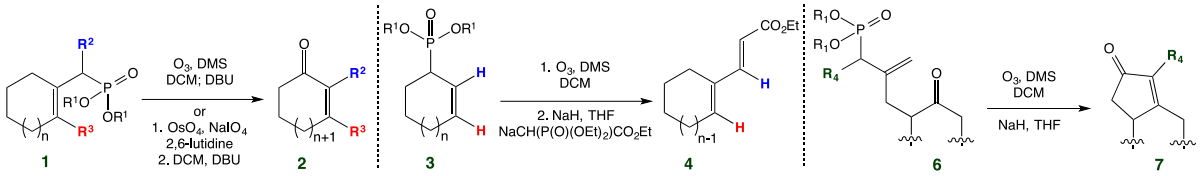
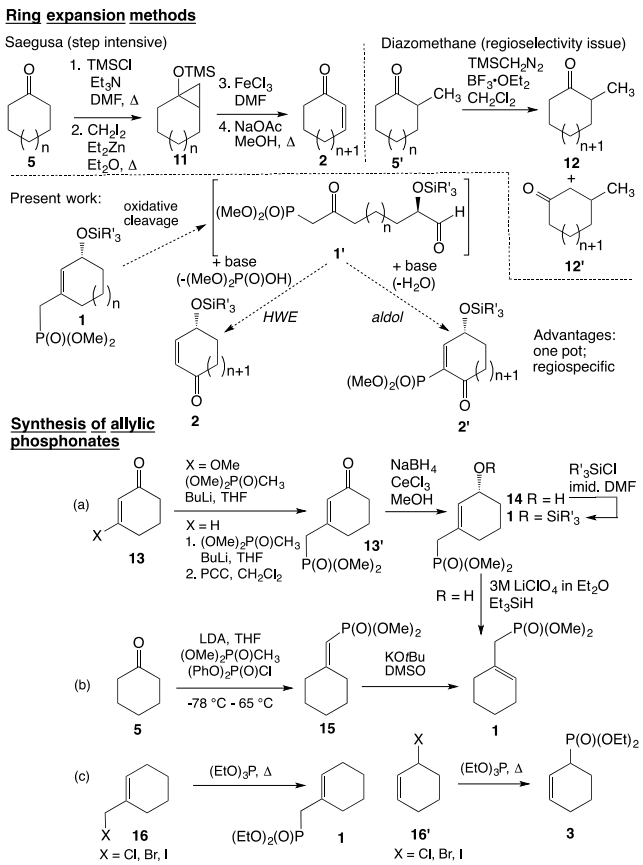
Supporting Information Placeholder



ABSTRACT: Oxidative cleavage of cycloalkenylalkylphosphonates **1** followed by treatment with base gives rise to homologated cycloalkenones **2** in good to excellent yields. Subjecting cycloalk-2-enylphosphonates **3** to identical conditions provides the one-carbon ring-contracted compounds **4** in excellent yields. Oxidative cleavage of γ□δ-unsaturated ketophosphonates **6** followed by treatment with base affords 2-cyclopenten-1-ones **7** in good overall yields. This method may offer a practical alternative to existing methods for effecting one-carbon ring expansion, ring contraction, and annulation reactions.

Ring expansion reactions are a useful synthetic means to access medium-ring carbocycles, which form the core of numerous natural products.[1] Two of the most popular methods for accomplishing this transformation include the Saegusa reaction,[2] involving the thermal or $FeCl_3$-mediated cleavage of silyloxy cyclopropanes, and the addition of diazomethane or its derivatives to cycloalkanones in the presence of Lewis acids (Scheme 1).[1b] Commencing from cyclic ketones, the Saegusa protocol involves multiple steps (silyl enol ether formation, cyclopropanation, oxidative cleavage, and elimination of chloride ion),[4] and many procedures combine these processes into just three separate tranformations.[5] Nonetheless, reactivity issues encountered for any one of the four steps may jeopardize overall yields for the homologation process. The diazomethane procedure typically suffers from low regioselectivity, though appropriate substitution patterns in the starting ketone substrate may lead to high yields of a single regioisomer.[3] Radical-based ring expansion reactions,[1d,e] proceeding via alkoxy-radical fragmentation of strained three-and four-membered ring intermediates, typically provide low yields of homologated products and sometimes require the use of toxic organostannane reagents. Clearly, there is a need for alternative procedures to achieve this important transformation.

Scheme 1. Synthesis and potential utility of allylic phosphonates.

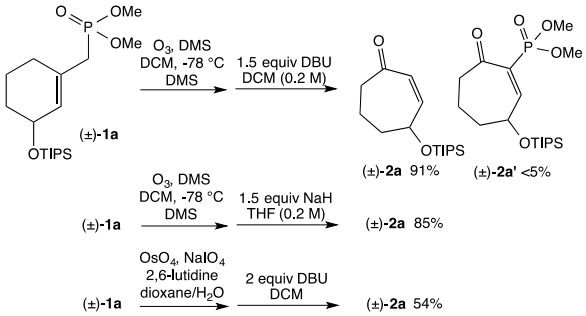


In attempting to access medium-ring enones as intermediates for natural product synthesis, it became apparent to us that intramolecular Horner-Wadsworth-Emmons (HWE) olefination reactions[6] were particularly suitable for the preparation of diversely substituted cycloheptenones from aldehyde-tethered β-ketophosphonates.[7] However, the synthesis of the requisite β-ketophosphonates from suitable acyclic starting materials required multiple steps and the preparation and isolation of an often unstable aldehyde intermediate. To circumvent these problems, we surmised that oxidative cleavage of a stable cyclic allylic phosphonate precursor would directly give rise to the β-ketophosphonate intermediate for the intramolecular olefination reaction; treatment with base would then provide the expanded cyclic enone product. However, intramolecular base-mediated condensation of β-ketophosphonates and aldehydes or ketones may form two different products (Scheme 1): cyclic enone **2** (arising from an intramolecular Horner-Wadsworth-Emmons reaction)[6] or cyclic β-ketophosphonate **2'** (arising from an intramolecular aldol condensation).[8] We believed that a judicious choice of base could control which homologated product predominated, with stronger bases favoring formation of enones of the type **2**. A benefit of this procedure over using acyclic starting materials is that investigators could take advantage of the numerous methods available for control of stereochemistry in cyclic systems to elaborate their substrates.[9] The success of this method would depend on the ease of synthesis of allylic phosphonates.

A variety of efficient methods are available for the preparation of cyclic allylic phosphonates. An addition of the anion of dimethyl methylphosphonate to cyclic enones, followed by oxidative transposition (PCC, CH_2Cl_2) gives rise to enone-β-phosphonates in high overall yields (a, Scheme 1);[10] the same products can be accessed directly by addition of lithiated dimethyl methylphosphonate to 3-methoxy-cycloalken-1-ones, followed by a reaction quench under acidic conditions.[11] Reduction of the ketone and protection of the alcohol or deoxygenation of the allylic alcohol[12] then provides allylic phosphonates suitable for one-carbon ring expansion. Alternatively, cyclic ketones can be condensed with *in situ* prepared β-diphosphonates to give vinyl phosphonates, which undergo base-mediated isomerization to allylic phosphonates in DMSO (b, Scheme 1).[13] Finally, halogenation of cyclic alkenes[14] or allylic alcohols[15] gives rise to halide substrates that undergo facile Michaelis-Arbuzov reactions[16] with phosphites to produce allylic phosphonates (c, Scheme 1).

With adequate methods available for the preparation of diverse allylic phosphonates, we first investigated oxidative cleavage and condensation conditions for the 6→7 ring expansion reaction (Scheme 2). Bubbling ozone through a solution of silyl ether **1a** in 1:1 DCM/MeOH at -78 °C for 15 minutes, followed by the addition of excess DMS and warming to room temperature resulted in complete consumption of the starting material by TLC analysis. Concentration of the reaction mixture to remove DMS and methanol, followed by addition of 1.5 equiv of DBU in anhydrous CH_2Cl_2 (0.2 M, 18 h, rt) resulted in clean conversion to the homologated enone **2a** in 91% yield after purification. No evidence for formation of aldol product **2a'** was seen by ^{1}H NMR of the crude reaction mixture. Similarly, it was found that after concentration of the ozonolysis reaction mixture, treatment with NaH (1.5 equiv) in dry THF (0.2 M, 18 h rt) also gave **2a** in 85% yield.

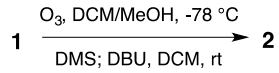
Scheme 2. Ring expansion of cyclic allylic phosphonate **1a** under oxidative cleavage conditions.



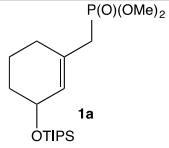
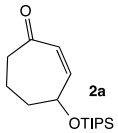
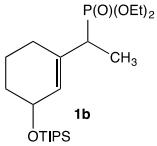
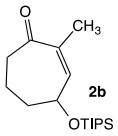
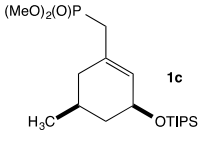
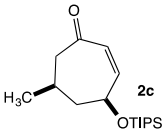
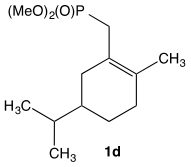
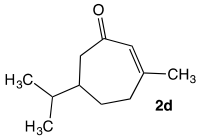
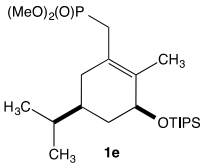
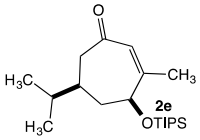
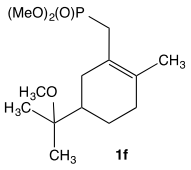
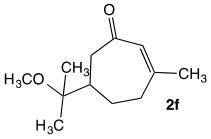
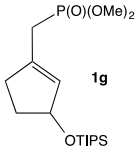
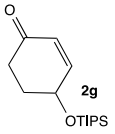
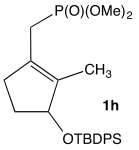
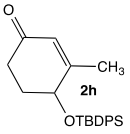
Treatment of **1a** instead with 2.5 mol % OsO_4 and $NaIO_4$ (3 equiv) in dioxane/H_2O (3:1) in the presence of 2,6-lutidine according to Jin's protocol[17] resulted in complete conversion of the starting material (within 3-12 hours) to multiple more polar compounds. An addition of anhydrous sodium sulfate to the reaction mixture, concentration *in vacuo*, and an addition of 1.5 equiv of DBU in DCM (0.2 M) gave rise to **2a**, which was isolated from the reaction mixture in 54% yield. Attempts to optimize the yields of **2a** obtained in this manner by decreasing reactions times, or using alternate solvents or stoichiometric oxidants ($PhI(OAc)_2$)[18] proved unsuccessful.

As shown in Table 1, the homologation process was successful for both 5-membered and 6-membered cyclic allylic phosphonates (**1a-1h**, produced from the corresponding 2-cyclohexen-1-ones and 2-cyclopenten-1-ones via pathway A, Scheme 1), giving rise to diverse 6- and 7-membered cyclic enones (**2a-2h**) in good to excellent yields. In entries 1-3, the ozone/DMS/DBU procedure provided superior yields to the OsO_4/$NaIO_4$/DBU protocol. It was found that both trisubstituted (**1a-1c**, **1g**) and tetrasubstituted (**1d-1f, 1h)** cyclic alkenes undergo the homologation process with similar efficiencies. Furthermore, the α-methyl enone **2b** could be prepared in 69% yield from α-methyl phosphonate **1b**, and β-methyl enones **2d-2f** and **2h** were available in 62-85% yields from phosphonates **1d**, **1e**, **1f** and **1h**, respectively.

Table 1. Scope of the ring expansion reactions of **1**.

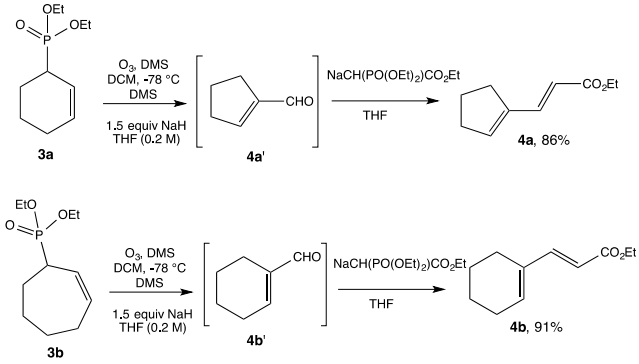


[a]Isolated yields after column chromatography. [b]Yield in parenthesis represents that obtained from oxidative cleavage of **1** with OsO_4, $NaIO_4$, and 2,6-lutidine (3:1 dioxane:water, rt, 24 h) followed by treatment with Na_2SO_4, filtration/concentration *in vacuo* and dilution with a solution of 1.5 equiv DBU in DCM (0.2 M).[c] Starting material and product obtained as a 3:1 mixture of *syn*:*anti* diastereomers. [d] Cyclization performed with NaH (1.5 equiv) in THF (0.2 M, rt, 12 h).

entry	1	2	yield **2**[a]
1			91(54)[b]
2			69(45)
3			85(53)[c]
4			71[d]
5			76[c]
6			62[d]
7			82
8			85

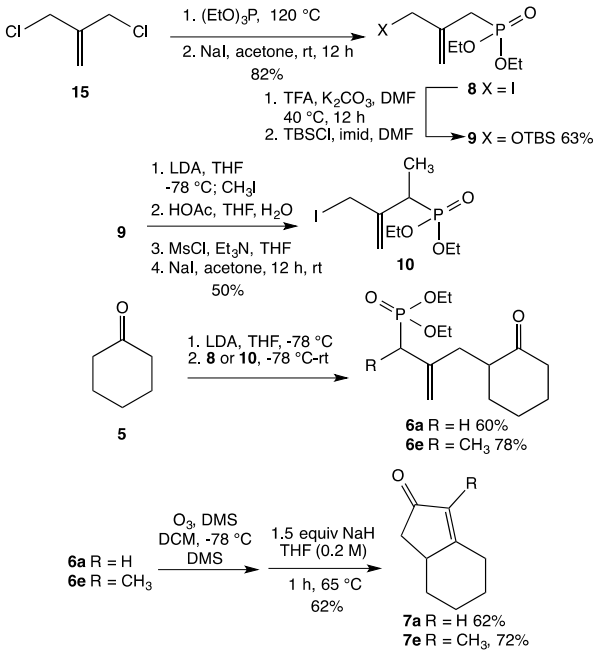
It was apparent that this process could also lead to ring contraction reactions[19] if the allylic carbon atom of the phosphonate was incorporated in a ring (Scheme 3). This possiblility was investigated with cyclic phosphonates **3a** and **3b**, readily avalable from 1-bromo-2-cyclohexene and 1-bromo-2-cycloheptene by a Michaelis-Arbuzov reaction (pathway C, Scheme 1).[16] Ozonolysis of **3a**, followed by concentration *in vacuo* and treatment with 1.5 equiv of NaH in THF produced the corresponding ring-contracted enal; due to extreme volatility, this compound was not isolated, but combined directly with the sodium salt of triethylphosphonoacetate to provide diene **4a** in 86% overall yield. A similar procedure applied to cycloheptenyl phosphonate **3b** gave diene **4b** in 91% yield.

Scheme 3. Ring contractions of allylic phosphonates **3**.



We further realized that this protocol might be of utility in the formation of cyclopentenones from ketones via an annulation-type process[20] employing a suitable allylic phosphonate alkylating agent (Scheme 4). Thus, commercially available 3-chloro-2-(chloromethyl)-1-propene was combined with triethylphosphite (120 °C, 12 h) to provide the corresponding phosphonate in quantitative yield; treatment of the crude allyl chloride with NaI in acetone for 12 hours gave iodide **8** in 82% overall yield. The α-methyl phosphonate **10** could also be prepared in 50% overall yield by methylation of silyl ether **9** (LDA, THF, -78 °C; CH_3I)[21] followed by silyl ether hydrolysis[22] and iodination. Exposure of the lithium enolate of cyclohexanone to **8** or **10** (THF, -78 °C, 30 minutes, then rt, 30 minutes) gave rise to the alkylated products **6a** and **6e** cleanly in 60 and 78% yields, respectively. Ozonolysis of **6a**, followed by treatment of the crude reaction mixture after concentration *in vacuo* with 1.5 equiv of NaH in THF at 65 °C for 1 h provided cyclopentenone **7a** in 62% yield; a similar treatment of **6e** produced **7e** in 72% yield.

Scheme 4. Synthesis and cyclopentannulation reactions of reagents **8** and **10**.



The two-step annulation process was explored with both cyclic (**6a, 6c-f**, Table 2) and acyclic (**6b**) ketones and was found to provide the corresponding 2-cyclopenten-1ones **7a-f** in good overall yields. Notably, this method also provides efficient access to 6-5 (**7e**) and 7-5 (**7f**) fused 2-methyl-2-cyclopenten-1-ones.[20b]

In summary, we have shown that cyclic allylic phosphonates may serve as precursors of ring-expanded or ring-contracted compounds via single-flask oxidative cleavage and base-promoted intramolecular Horner-Wadsworth-Emmons reactions. In addition, alkylation of cyclic and acyclic ketones with iodides **8** or **10**, followed by oxidative cleavage and base treatment of the intermediate γ□δ-unsaturated ketophosphonates, furnishes 2-cyclopenten-1-ones in good overall yields by an annulation-type process. Application of these procedures to the total synthesis of guaiane sesquiterpene natural products (see Figure 1) is currently in progress and will be reported in due course.

Figure 1. Some guaiane sesquiterpene natural products possessing fused 7-5 ring systems potentially accessible by this methodology.

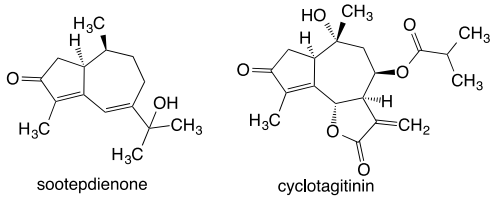
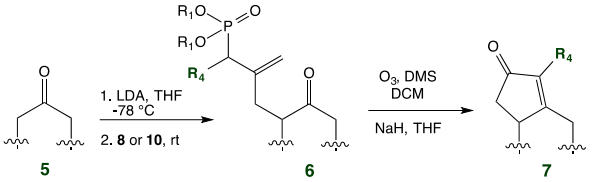


Table 2. Cyclopentannulations with phosphonates **8** and **10**.



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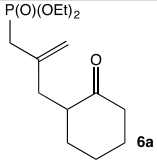
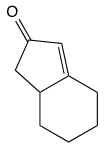
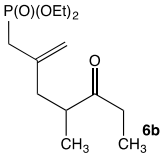
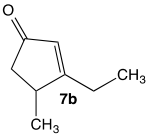
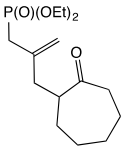
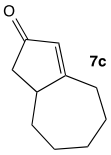
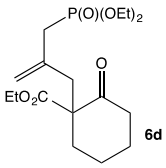
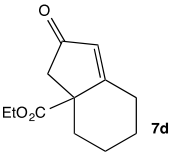
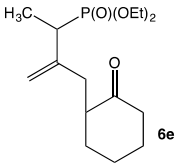
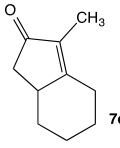
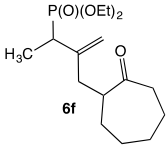
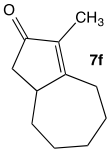
1	 6a	60	 7a	62
2	 6b	71	 7b	81
3	 6c	91	 7c	88
4	 6d	51	 7d	59
5	 6e	78[b]	 7e	72
6	 6f	66[b]	 7f	80

[a]Isolated yields after column chromatography. [b] Starting material obtained as a 1:1 mixture of diastereomers.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds in Tables 1 and 2 and Schemes 3 and 4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through the contributions of all authors.

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REFERENCES

1. For reviews, see: (a) Donald, J. R.; Unsworth, W. P. *Chem. Eur. J.* **2017**, *23*, 8780. (b) Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem Rev.* **2016**, *116*, 2937. (c) Roxburgh, C. J. *Tetrahedron*, **1993**, *49*, 10749. (d) Dowd, P.; Zhang, W. *Chem Rev.* **1993**, *112*, 66. (e) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (f) Kantotowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317.
2. Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth.* **1980**, *59*, 113.
3. (a) Kreuzer, T.; Metz, P. *Eur. J. Org. Chem.* **2008**, 572. (b) Uyehara, T.; Kabasawa, Y.; Kato, T.; Furuta, T. *Tetrahedron Lett.* **1985**, *26*, 2343.
4. Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.
5. (a) Paquette, L. A.; Ham, W. H.; Dime, D. S. *Tetrahedron Lett.* **1985**, *26*, 4983. (b) Blake, A. J.; Highton, A. J. ; Majid, T. N.; Simpkins, N. S. *Org Lett.* **1999**, *1*, 1787.
6. (a) Kaori, A.; Narumiya, K.; Takada, H.; Teruya, T. *Tetrahedron Lett.* **2011**, *52*, 1284. (b) Kaori, A.; Narumiya, K.; Takada, H.; Teruya, T. *Org. Lett.* **2010**, *12*, 1460. (c) Krawczyk, H.; Albrecht, L. *Synthesis* **2008**, *24*, 3951. (d) Nangia, A.; Prasuna, G.; Bheema, R. P. *Tetrahedron Lett.* **1994**, *35*, 3755. (e) Saya, J. M.; Vos, K.; Kleinnijenhuis, R. A.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Org. Lett.* **2015**, *17*, 3892. (f) Hubert, J. G.; Furkert, D. P.; Brimble, M. A. *J. Org. Chem.* **2015**, *80*, 2231. (g) Donslund, B. S.; Halskov, K. S.; Leth, L.A. Paz, B. M.; Jorgensen, K. A, *Chem. Commun.* **2014**, *50*, 13676. (h) Pirrung, M. C.; Biswas, G.; Ibarra-Rivera, T. R. *Org. Lett.* **2010**, *12*, 2402. (i) Chen, C.-A.; Fang, J.-M. *Org. Biomol. Chem.* **2013**, *11*, 7687.
7. Pan, S.; Gao, B.; Hu, J.; Xuan, J.; Xie, H.; Ding, H. *Chem. Eur. J.* **2016**, *22*, 959.
8. Wada, E.; Funakoshi, J.; Kanemasa, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2456.
9. Stereochemical Control in Cyclic and Polycyclic Systems. In *Organic Chemistry in Action: the Design of Organic Synthesis*; Serratosa, F., Ed.; Elsevier Science: New York, 1990; Chapter 8.
10. (a) Mphahlele, M. J. *Phosphorous, Sulfur and Silicon and the Related Elements* **1996**, *118*, 145. (b) Hudlicky, J. R.; Werner, L.; Semak, V.; Simionescu, R.; Hudlicky, T. *Can. J. Chem.* **2011**, *89*, 535.
11. Mphahlele, M. J.; Modro, T.A. *J. Org. Chem.* **1995**, *60*, 8236.
12. Wustrow, D. J.; Smith, W. J.; Wise, L. D. *Tetrahedron Lett.* **1994**, *35*, 61.
13. Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572.
14. Marvel, C.S.; Hartzell, G.E. *J. Am. Chem. Soc.* **1959**, *81*, 448.
15. Hazelden, I. R.; Ma, X.; Langer, T.; Bower, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 11198.
16. (a) Michaelis, A.; Kaehne, R. *Berichte* **1898**, *31*, 1048. (b) Arbuzov, A. E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.
17. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
18. Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552.
19. (a) Silva, L. F. *Synlett*, **2014**, *25*, 466. (b) Song, Z.–L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, 7523. (c) Silva, L. F. *Tetrahedron*, **2002**, *58*, 9137. (d) Silva, L. F. *Molecules*, **2006**, *11*, 421.
20. (a) Welch, S.C.; Assercq, J. M.; Loh, J. P. Glase, S. A. *J. Org. Chem* **1987**, *52*, 1440. (b) Piers, E.; Abeysekera, B. *Can. J. Chem.* **1982**, *60*, 1114. (c) Altenbach, H. J. *Angew. Chem.* **1979**, *91*, 1005. (d) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175.
21. Nagase, T.; Kawashima, T.; Inamoto, N. *Chem. Lett.* **1984**, *11*, 1997.
22. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.