ORGANIC LETTERS

2001
Vol. 3, No. 18
2819−2821

Intramolecular [2 + 2]-Photocycloaddition/Thermal Fragmentation Approach toward 5–8–5 Ring Systems

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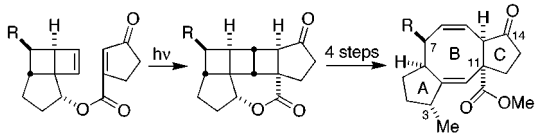
Received June 7, 2001

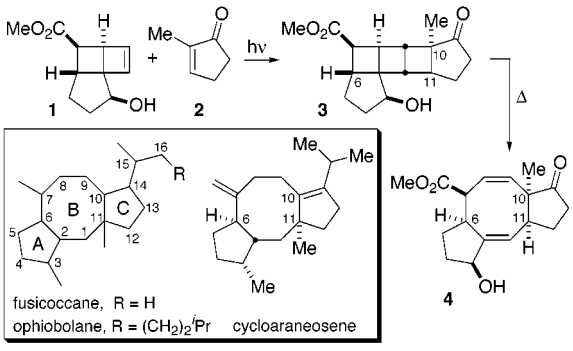
ABSTRACT



An intramolecular [2 + 2]-photocycloaddition is used to provide a photoadduct, which upon fragmentation, lactone cleavage, and subsequent Cope rearrangement provides a dicyclopenta[*a*,*d*]cyclooctene ring system with substituents in place (e.g., C3 and C11) to access several 5–8–5 diterpene and sesterterpene natural products.

We reported recently a new method for constructing the dicyclopenta[*a*,*d*]cyclooctene (5−8−5) ring system[1] observed in several classes of natural products such as the fusicoccanes and ophiobolanes[2] (Scheme 1). The key features of the strategy include a regio- and stereoselective intermolecular [2 + 2]-photocycloaddition between functionalized cyclobutenes[3] (**1**) and cyclopentenones (**2**), followed by thermal fragmentation of the resulting strained photoadducts (**3**).[4] The reaction sequence provides the target 5−8−5 ring system (**4**) in as few as seven steps, with functionality in place to access several natural product targets including the appropriate stereochemistry at the C6 ring fusion. Notwithstanding this rapid entry into the ring system, the installation of a carbon substituent commonly found at C11 still requires significant synthetic effort. The results reported herein offer an improved strategy for generating the 5−8−5 ring system with the requisite alkyl substituent at C11.

Scheme 1. 5-8−5 Natural Product Ring Systems Compared to the Intermolecular Photocycloaddition/Fragmentation Product 4



(1) (a) Randall, M. L.; Lo, P. C-K.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534−4535. For reviews on [2 + 2]-photocycloaddition/fragmentation strategies, see: (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003−2020. (c) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453−1473.

(2) (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (b) Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343−2364.

(3) (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197. (b) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440−6441. For recent related applications of cyclobutadiene generated cyclobutenes, see: (c) Limanto, J. L.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071−8072. (d) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152−5153.

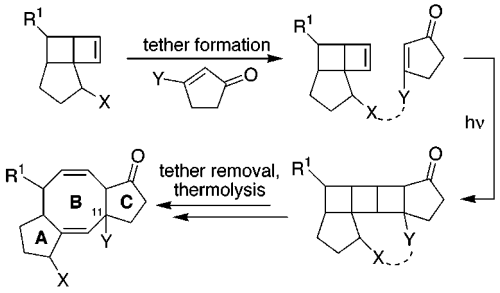
(4) For related examples, see: (a) White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665−8671. (b) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4321−4322.

10.1021/ol016244l CCC: $20.00
Published on Web 08/10/2001

Because the [2 + 2]-photocycloaddition controls the introduction of substituents at C10 and C11, efforts to influence the regiochemistry using other cyclopentenones were pursued. Photocycloaddition of cyclobutene **1** with 3-methylcyclopentenone, for example, provides a photoadduct with the methyl substituent at C10 instead of C11 (data not shown). In all cases, the larger functionality in either the α- or *β*-position on the cyclopentenone is placed in the less hindered C10 site in the intermolecular photocycloaddition.

Given these observations, an *intramolecular* transformation was expected to overcome the inherent steric preference observed in the intermolecular process. As illustrated in Scheme 2, a temporary tether between the cyclobutene and

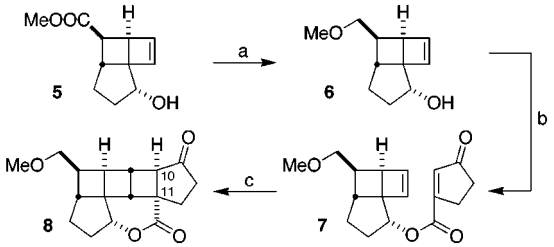
Scheme 2. Intramolecular Photocycloaddition/Thermal Fragmentation Approach to 5−8−5 Ring Systems



the cyclopentenone could enforce the desired regioselectivity and thereby introduce the necessary alkyl substituent (R^3) at C11 in the BC ring junction.

As illustrated in Scheme 3, photoprecursor **7** was prepared from cyclobutene **5**[5] to evaluate the intramolecular strategy.

Scheme 3. Synthesis of Tethered Cyclobutene **7** and Intramolecular Photoadduct **8**[a]

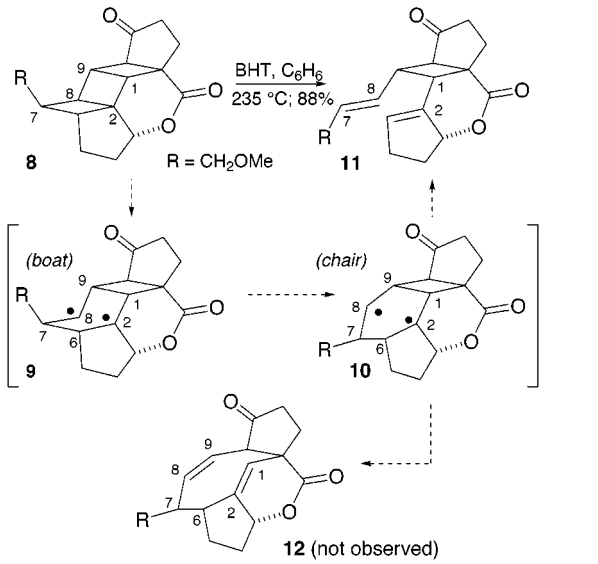


[a] (a) (i) TBDPSCl, imidazole, Et_3N, CH_2Cl_2, rt, 91%; (ii) $LiAlH_4$, Et_2O, 0 °C; (iii) NaH, THF, rt; MeI, THF, rt; (iv) TBAF, THF, rt, 93% (3 steps). (b) 3-oxo-cyclopent-1-ene-carboxylic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 91%. (c) *hν*, Pyrex filter, C_6H_6, 40 °C, 93%.

Although reduction of cyclobutene **5** followed by selective methylation of the resulting diol is possible, higher yields of compound **6** were obtained through a four-step sequence that included protection and deprotection of the secondary alcohol. A DCC-mediated esterification of **6** with 3-oxo-cyclopent-1-ene-carboxylic acid[6] afforded the cyclopentenone-tethered cyclobutene **7** in 91% yield.[7] Intramolecular [2 + 2]-photocycloaddition of **7** using a medium pressure Hanovia Hg-lamp with a Pyrex filter occurred smoothly to give the highly strained photoadduct **8** (93%). This cycloadduct possesses the essential one-carbon functionality at the desired ring junction position (C11).

Thermolysis of photoadduct **8** was carried out at 235 °C in benzene (Scheme 4). Instead of generating *cis,trans*-1,5-

Scheme 4. Thermolysis of Photoadduct **8**



cyclooctadiene **12**, the thermodynamically more favored dialkenyl cyclobutane **11** was produced in 88% yield. The formation of compound **11** with an *trans*-olefin (C7−C8) is consistent with a mechanistic model described previously for the fragmentation reaction.[1] Cleavage of the strained C2−C8 bond in photoadduct **8** can form diradical **9**, which can either collapse to regenerate **8** or relax to a cyclohexadiyl in a chair conformation **10**.[8] Intermediate **10** can then lead to either compound **12** through cleavage of the C1−C9 bond (which can then provide compound **11** through a Cope rearrangement) or directly to compound **11** through cleavage of the C6−C7 bond. Evidently, formation of any cyclooctadiene products, either directly from diradical **10** or through a Cope rearrangement of compound **11** is inhibited by the geometric constraints imposed by the lactone.[9]

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(6) Herzog, H.; Koch, H.; Scharf, H.-D.; Runsink, J. *Tetrahedron* **1986**, *42*, 3547−3558.

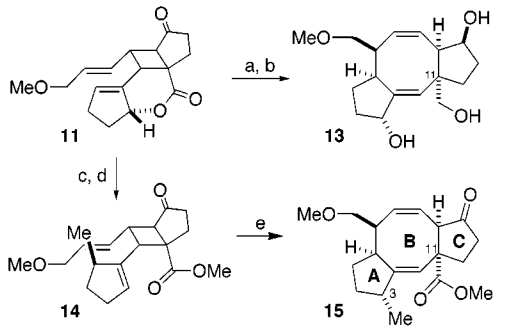
(7) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475−4478.

(8) Orbital symmetry preferences argue against the formation of products resulting from the *direct* cleavage of diradical **9**. (a) Wiberg, K. B.; Caringi, J. J.; Matturro, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 5854−5861. (b) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 5119−5121. (c) Paquette, L. A.; Schwartz, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 3215−3217. (d) Roth, W. R.; Martin, M. *Tetrahedron Lett.* **1967**, 3865−3866.

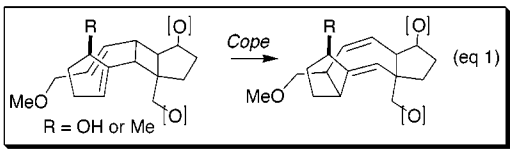
Formation of the desired 5−8−5 ring system therefore requires cleavage of the lactone functionality.

As illustrated in Scheme 5, reduction of lactone **11** followed by heating the resulting triol provides cyclooctadiene **13**, a compound with the target 5−8−5 ring system and an alkyl substituent at C11. The boatlike conformation expected to be responsible for the stereospecific Cope rearrangement of the dialkenyl cyclobutane is shown in eq 1.[10] The *bis-endo* conformation of the olefins allows for the selective formation of the observed *cis,cis*-1,5-cyclooctadiene product **13**.

Scheme 5. Generation of 5−8−5 Products **13** and **15**[a]



(a) $LiAlH_4$, 53%; (b) C_6H_6, 140 °C, 94%; (c) MeMgBr, $CuBr{\cdot}Me_2S$, Me_2S, THF, -20 °C; **11**, 66% 14:1 dr; (d) $TMSCHN_2$, MeOH/PhH, r.t., 93%; (e) C_6H_6, BHT, 120 °C, 96%.



[a] (a) LiAlH4, 53%; (b) C_6H_6, 140 °C, 94%; (c) MeMgBr, $CuBr{\cdot}Me_2S$, Me_2S, THF, −20 °C; **11**, 66% 14:1 dr; (d) $TMSCHN_2$, MeOH/PhH, rt, 93%; (e) C_6H_6, BHT, 120 °C, 96%.

Alternatively, cleavage of the allylic lactone and direct installation of an A ring methyl group at C3 in a single step was also explored. Since methyl organocopper reagents displace allylic acetates in a regio- and stereoselective fashion,[11] this strategy was examined in the allylic lactone opening/alkylation of substrate **11**. On the basis of NMR studies of the 5−8−5 product **15**, the nucleophilic attack of the methyl group on lactone **11** appeared to have occurred predominantly in a S_N2' fashion, *anti* with respect to the carboxylate leaving group as expected from prior studies.[11] Treatment of the resulting carboxylic acid with trimethylsilyldiazomethane generates methyl ester **14** in 61% overall yield from **11**.[12] Thermal rearrangement of cyclobutane **14** produces compound **15** in 96% yield with the desired C3 methyl group installed on the A ring and an ester at C11 in the corresponding 5−8−5 natural product framework. Again, the conformation for the stereospecific Cope rearrangement of cyclobutane **14** is shown in eq 1.

In summary, we have illustrated that an *intramolecular* [2 + 2]-photocycloaddition of a tethered cyclobutene (**7**) can be used to introduce the necessary alkyl functionality at the C11 position in the 5−8−5 ring system. The intramolecular photocycloaddition produces a highly strained photoadduct **8** that leads to a dialkenyl cyclobutane intermediate **11** upon thermal fragmentation. Cleavage of the allylic ester in compound **11**, followed by Cope rearrangement delivers the core sequiterpenoid 5−8−5 ring structure with functionality in place to access several natural product targets. Studies toward this goal are currently underway.

Acknowledgment. We are grateful to the NSF, ACS-PRF for generous support of this research.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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