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# Oxabicyclo[3.2.1]octenes in Organic Synthesis—Direct Ring Opening of Oxabicyclo[3.2.1] Systems Employing Silyl Ketene Acetals in Concentrated Solutions of Lithium Perchlorate–Diethyl Ether: Application to the Synthesis of the C(19)–C(27) Fragment of Rifamycin S

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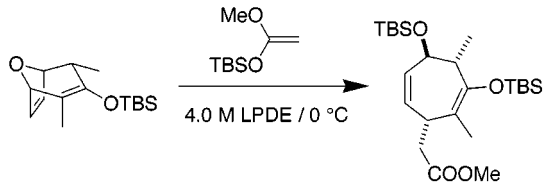
## ABSTRACT




**The direct opening at the bridgehead of oxabicyclo[3.2.1]octenes employing silyl ketene acetals in 4.0–5.0 M lithium perchlorate in diethyl ether has been realized, which gives rise to highly functionalized cycloheptadienes that can be further manipulated for use in natural product synthesis. The bridgehead opening reaction has been employed in the construction of the C(19)–C(27) fragment of Rifamycin S.**

The use of rigid oxabicyclo[3.2.1]octenes as stereochemical control vehicles in organic synthesis has received only limited attention despite the potential such ring systems hold for those engaged in natural products synthesis. Despite the reported successes employing 8-oxabicyclo[3.2.1]octenes,[1,2] where stereochemical information built into the oxabicyclo-[3.2.1] system was transformed into acyclic and cyclic molecules rich in stereogenic centers, efforts to selectively introduce substituents into the bridgehead positions have met with no success. Lautens[2,3] recognized the importance of carrying out such transformations; however, he has shown that the predominant mode of attack in such systems is $S_N2'$ syn. We detail below a solution to this problem featuring the direct bridgehead opening of oxabicyclo[3.2.1]octadienes (cf. **1**) with 1-methoxy-1-(*tert*-butyldimethylsiloxy)-ethylene in 4.0−5.0 M lithium perchlorate−diethyl ether (LPDE).[4,5]

(1) (a) White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226. (b) Rama Rao, A. V.; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55. (c) Lautens, M.; Belter, R. K. *Tetrahedron Lett.* **1992**, *33*, 2617.

(2) Lautens, M. *Synlett* **1993**, 177.

(3) Lautens, M. *Pure Appl. Chem.* **1992**, *64*, 1873. Woo, S.; Keay, B. A. *Synthesis* **1996**, 669.

(4) For the use of highly polar media to promote organic reactions, see: Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59. Grieco, P. A. Organic Chemistry in Lithium Perchlorate/Diethyl Ether. In *Organic Chemistry: Its Language and Its State of the Art*; Kisakürek, V., Ed.; VCH: Basel, 1993; p 133.

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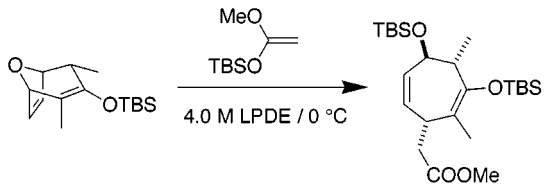
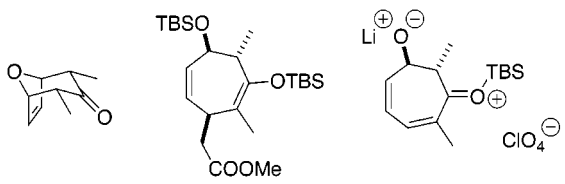
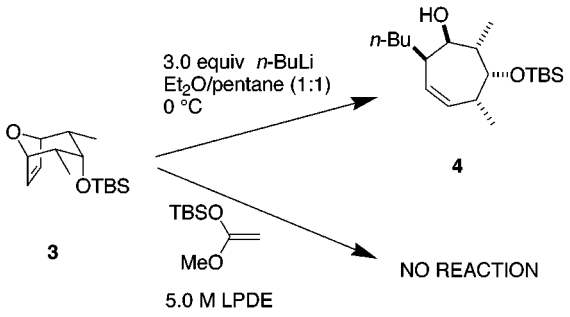



1 2a




5 2b 6

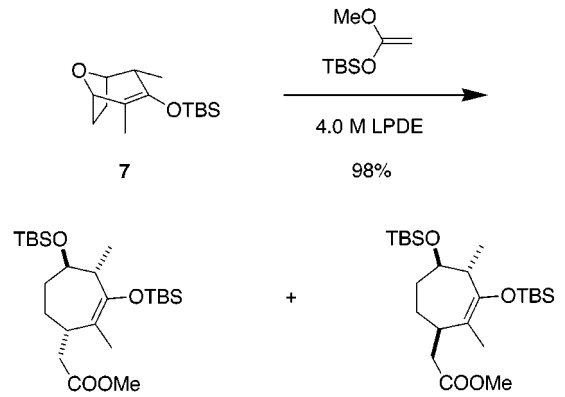
The ready availability[6] of strained bicyclic molecules such as 8-oxabicyclo-[3.2.1]octene **3** makes them useful templates for organic synthesis. In this regard, we set out to effect ring opening at the bridgehead of oxabicyclic compounds such as **3** in hopes of further exploiting these highly functionalized systems for use in natural products synthesis. Whereas it has been previously shown the treatment of **3** with *n*-butyllithium in ether/pentane (1:1) at 0 °C gives rise to the $S_N2'$ syn product **4** exclusively,[7] exposure of **3** to a silyl ketene acetal in 5.0 M LPDE provided only recovered starting material. Employment of traditional Lewis acids (boron trifluoride etherate, titanium tetrachloride, magnesium bromide) returned only **3** or resulted in loss of the silyl protecting group. Examination of molecular models reveals that overlap of the $\sigma^*$ orbital of the carbon−oxygen bond of the oxa bridge with the $\pi$ system of the olefin is minimal. It appeared that introduction of an additional $\pi$ system (cf. **1**) would give rise to enhanced overlap with the $\sigma^*$ orbital and thus render the process more favorable.



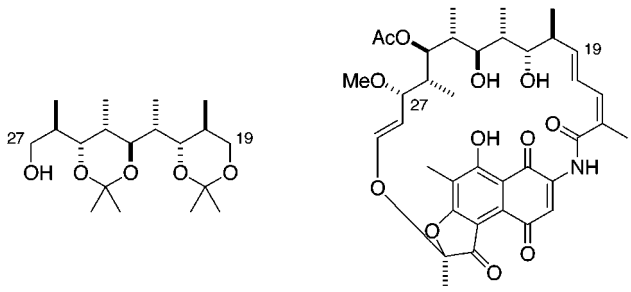

Thus, treatment of silyl enol ether **1**, generated [LDA, THF, HMPA, TBSCl] in near quantitative yield from ketone **5**,[8] with 2.0 equiv of 1-methoxy-1-(*tert*-butyldimethylsiloxy)-ethylene in 5.0 M LPDE at ambient temperature provided substituted cycloheptadienes **2a** and **2b** in a ratio of 4:1 in quantitative yield.[9] This ratio could be improved to 4.8:1 by performing the reaction in 4.0 M LPDE at 0 °C. Further attempts to improve the selectivity by attenuating the solvent polarity by using 3.0 M LPDE and 3.0 M lithium perchlorate−ethyl acetate were unsuccessful and led to incomplete conversion. Traditional Lewis acids gave rise to recovered starting material or ketone **5**.

The selectivity of the bridgehead addition proved to be substrate-dependent. As illustrated in Table 1, the facial bias ranges from exclusive α attack to being completely non-selective. In three of the five examples cited in Table 1, 5.0 M LPDE was employed because the reaction rates in 4.0 M LPDE were sluggish. In view of the stereochemical outcome of the reactions depicted in Table 1, it is unclear what type of mechanism is operational. The observation that the *tert*-butyldimethyl silyl ether **3** fails to react may well suggest the intermediacy of an extended oxocarbenium ion such as **6**.

Whereas substrate **3** proved to be unreactive in 5.0 M LPDE, exposure of silyl enol ether **7,** lacking the $\Delta^{6,7}$ olefin, to 1-methoxy-1-(*tert*-butyldimethylsiloxy)ethylene in 4.0 M LPDE afforded, after 1 h at ambient temperature, a 98% yield of **8** and **9** in a ratio of 10:1.




The operational simplicity of the bridgehead opening reactions, coupled with the ready availability of oxabicyclo-[3.2.1]octenones, prompted us to demonstrate the utility of this methodology by transformation of cycloheptadienyl ester **2a** into the C(19)−C(27) fragment **10** of Rifamycin S (**11**).




10 11

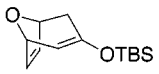
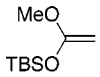
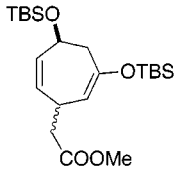
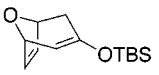
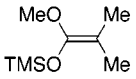
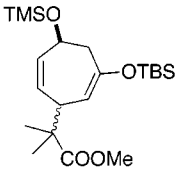
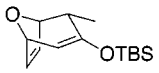
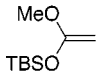
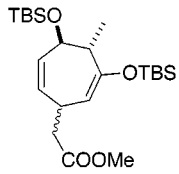
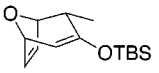
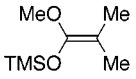
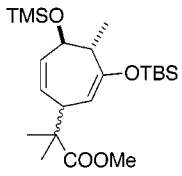
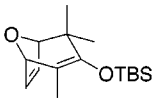
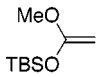
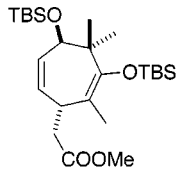
(5) For the direct bridgehead opening of a 2-methylthio-7-oxabicyclo-[2.2.1]hept-2-ene derivative with a silyl ketene acetal in the presence of TBSOTf and 4 Å MS, see: Yamamoto, I.; Narasaka, K. *Chem. Lett.* **1995**, 1129.

(6) Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976. Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765. Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.

(7) Lautens, M.; Belter, R. K. *Tetrahedron Lett.* **1992**, *33*, 2617.

(8) Ashcroft, M. R.; Hoffmann, H. M. R. *Org. Synth.* **1978**, *58*, 17.

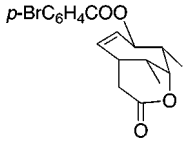
**Table 1.** Ring Opening of Oxabicyclo[3.2.1] Systems Employing Silyl Ketene Acetals[a]

| substrate | silyl ketene acetal | conditions[b] | product(s) | yield[c] (%)(α:β) |
|---|---|---|---|---|
|  |  | A / 4h |  | 95 (3:1) |
|  |  | B / 3h |  | 76 (1.5:1) |
|  |  | A / 4h |  | 91 (1:1) |
|  |  | B / 48h |  | 81 (1:11) |
|  |  | B / 1.5h |  | 60 |

[a] All reactions were performed 0.2 M in substrate in 4.0 or 5.0 M LPDE at ambient temperature employing 2.0 equiv of silyl ketene acetal. [b] Method A: 4.0 M LPDE. Method B: 5.0 M LPDE. [c] Isolated yields.

Exposure of cycloheptadienyl ester **2** to tetra-*n*-butylammonium fluoride (HOAc, THF, 60 h) provided (98%) cycloheptenone **12** (Scheme 1), which upon reduction, iodolactonization, and deiodination afforded bicyclic lactone **13** in 80% overall yield. Selective silylation of the C(25) hydroxyl, followed by dianion formation and alkylation with methyl iodide, gave rise to **14** as the sole product. Benzylation of the hindered C(23) hydroxyl and subsequent reduction of the lactone carbonyl provided diol **15**, which upon silylation of the primary hydroxyl, Ley oxidation,[10] and desilylation generated hemiketal **16**. Direct subjection of hemiketal **16** to Baeyer−Villiger oxidation conditions[11,12] followed by exposure of the resulting lactones to potassium

(9) The structure of **2a** was confirmed by conversion of **2a** into the crystalline *p*-bromobenzoate **i**, whose structure was confirmed by single-crystal X-ray analysis.

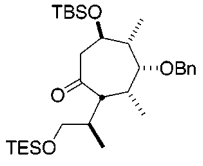


**i**

(10) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun*. **1987**, 1625. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

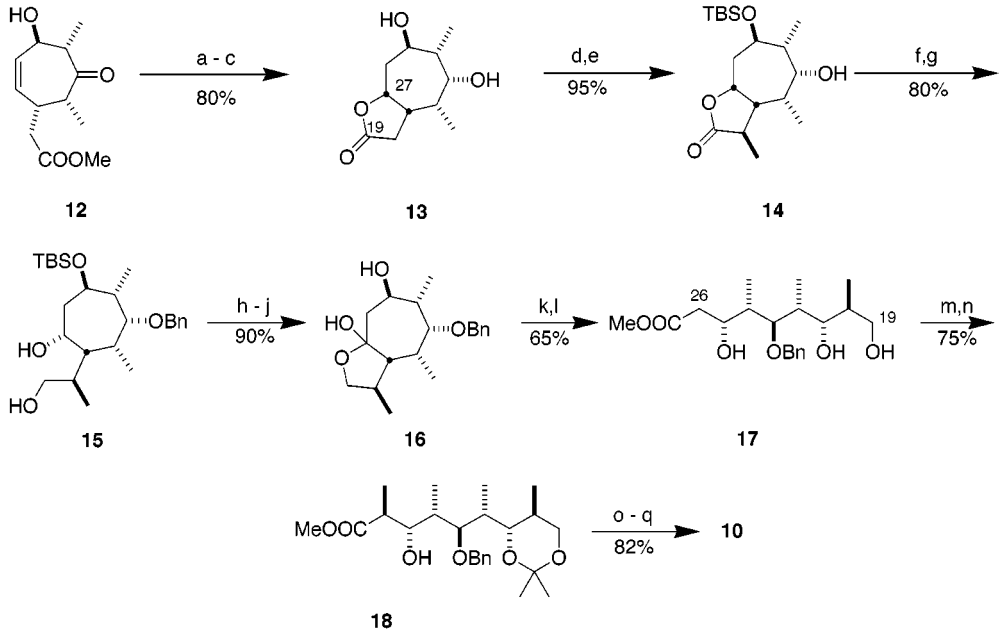
(11) Hunt, K. W.; Grieco, P. A. *Org. Lett*. **2000**, *2*, 1717.

(12) Attempts to perform the Baeyer−Villiger oxidation on ketone **ii** or similar substrates met with no success (see ref 11).



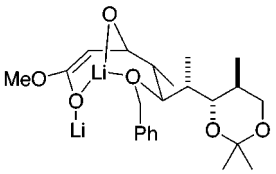
**ii**

**Scheme 1**[a]




[a] Conditions: (a) LiAl(O-*t*-Bu)$_3$H, THF, −20 °C, 20 h; (b) NaOH, THF, MeOH, $H_2O$; $CO_2$; KI/$I_2$, 0 °C; (c) $Bu_3SnH$, THF, AlBN, 60 °C, 2 h; (d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$; (e) LDA, THF, MeI, 0 °C; (f) KH, 18-C-6, BnBr, $Bu_4NI$, DMF, −10 °C, 1 h; (g) $LiBH_4$, THF, 36 h; (h) TESCl, 2,4,6-collidine, $CH_2Cl_2$, −78 °C, 30 min; (i) TPAP, NMO, $CH_2Cl_2$, 4 h; (j) TBAF, HOAc, THF; 0 °C, 12 h; (k) MCPBA, $CH_2Cl_2$, 4 h; (l) $K_2CO_3$, MeOH, 0 °C, 1 h; (m) 2,2-DMP, PPTS, DMF, 4 h; (n) LDA, THF, MeI, −78 → −5 °C, 1 h; (o) $H_2$, 10% Pd/C, absolute EtOH, 6 h; (p) 2,2-DMP, PPTS, $CH_2Cl_2$, 12 h; (q) $LiAlH_4$, $Et_2O$, 1 h.

carbonate in methanol gave rise to ester **17**. Acetonide formation and subsequent installation of the C(20) methyl group employing the Fráter−Seebach protocol[13] provided **18** as a single diastereomer. This remarkably selective alkylation can be rationalized by chelation of the benzyloxy group to form the rigid bicyclic structure **19**.[14] Cleavage of the benzyl ether, followed by acetonide formation and reduction of the ester afforded the C(19)−C(27) fragment of Rifamycin S. The spectra of **10** were identical in all respects with those reported in the literature.[15]




**19**

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR spectra for **1**, **2a**, **2b**, **7**, **8**, **10**, **12**−**15**, **17**, **18**, **i**, **ii** and ring-opened products from Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0003836

(13) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825. Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.

(14) A similar substrate capable of forming this type of rigid structure also provided a single alkylation product; see: Williams, D. R.; Rojas, C. M.; Bogen, S. L. *J. Org. Chem.* **1999**, *64*, 736.

(15) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637.