Pergamon

Tetrahedron Letters 42 (2001) 6019–6021

TETRAHEDRON
LETTERS

Convenient annulation of bicyclo[6.3.0]undecanes†

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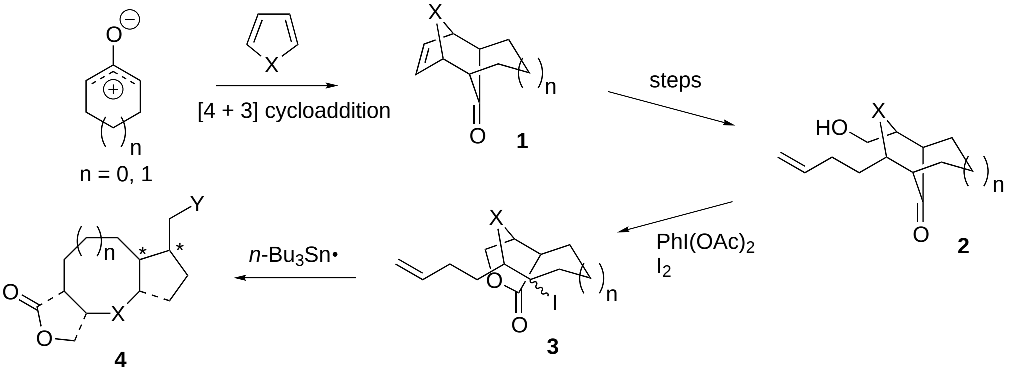
Received 30 May 2001; accepted 26 June 2001

Abstract—A facile, albeit nonstereoselective, method for the construction of a bicyclo[6.3.0]undecane skeleton has been developed by sequential application of the Suárez cleavage and 5-*exo* radical cyclization on the readily available [4+3] cycloadducts of cyclic oxyallyls. © 2001 Elsevier Science Ltd. All rights reserved.

The presence of bicyclo[5.3.0]decane and bicyclo[6.3.0]-undecane skeletons characterizes many naturally occurring terpenes and presents considerable synthetic challenges due to unfavorable entropic and enthalpic factors.[2] Development of efficient annulation methods for the medium-sized carbocycles has been an active area of research. We previously reported the preparation of functionalized seven- and eight-membered carbocycles and heterocycles by means of the [4+3] cycloaddition of *cyclic* oxyallyls (and related aminoallyls) and subsequent Suárez cleavage (**2**→**3**) of the ketone bridge.[3] Radical cyclization of the resulting iodide **3** to a suitably tethered olefin presented itself as a potentially convenient entry to 5,7- or 5,8-fused tricyclic rings **4** (Eq. (1)). As a preliminary synthetic study toward structurally complex natural products, we herein report a convenient construction of fused 5,8-bicyclic rings by sequential application of the Suárez cleavage and 5-*exo* radical cyclization starting from the [4+3] cycloadducts **1** ($n=1$).

Of particular interest is the little known diastereoselectivity of the transformations **3**→**4**; in contrast to a large body of data available on venerable 5-hexenyl cyclizations of five- and six-membered ring radicals, as well as acyclic radicals, there remains a paucity of examples concerning those of radicals embedded in the larger, conformationally flexible medium-sized rings.[4]

Our synthesis started from the [4+3] cycloadducts **1a**,**b**, which were converted to the alcohols **5a**,**b** by standard methods (Scheme 1).[3,5] At the outset, we chose to introduce a stereocenter in the butenyl side chain by addition of an allylmetal reagent to the aldehyde derived from **5a**,**b** so as to evaluate the substituent effects on diastereoselectivity of 5-*exo* radical cyclizations. Thus, Swern oxidation of **5a**, followed by addition of the allylindium reagent, gave a 4:5 mixture of **6** and **7** in 90% yield.[7] In any event, separation[8] and standard functional group manipulation of **6** and **7** then furnished **8** and **9**, the requisite substrates for Suárez



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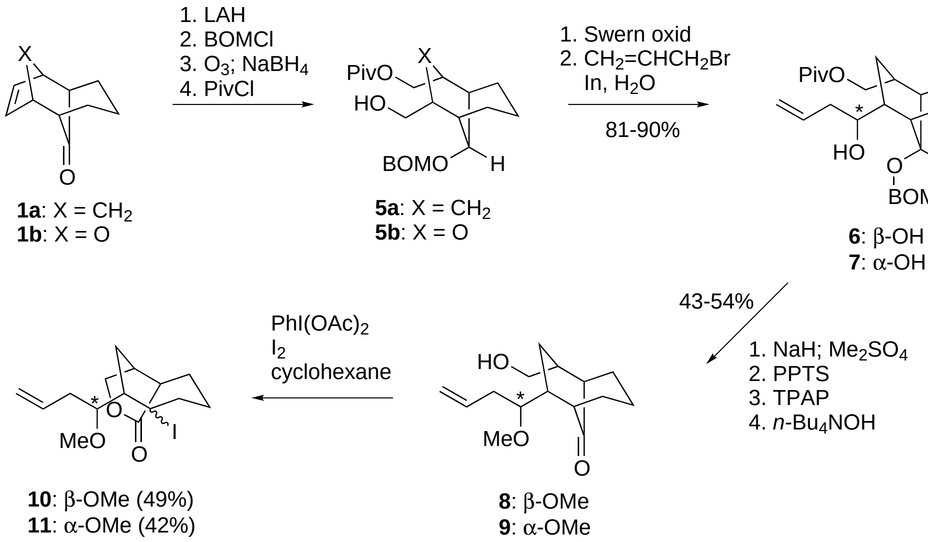
† See Ref. 1.

PII: S0040-4039(01)01184-4



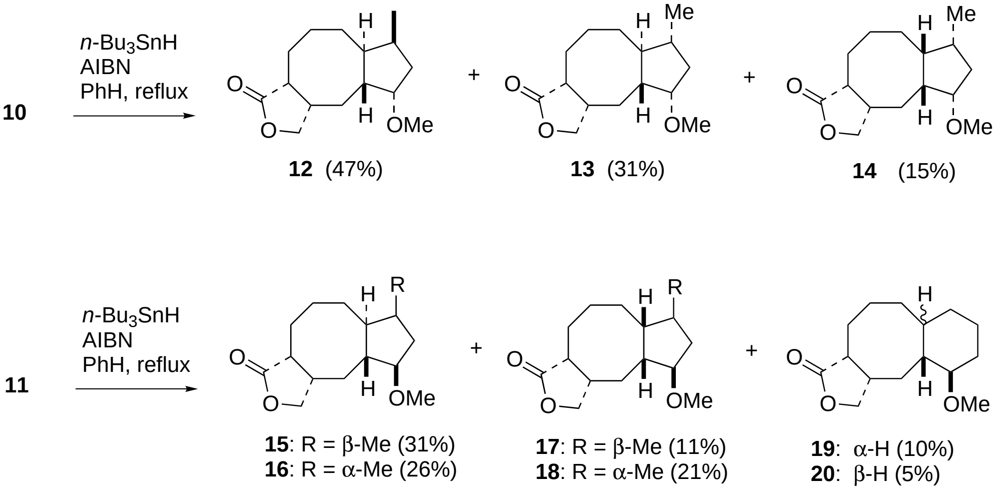
Scheme 1.

cleavage, respectively. Their unequivocal stereochemical determination was secured later by X-ray crystallographic analysis of the resulting cyclization products (vide infra).

Irradiation (100 W lamp, 40°C, cyclohexane) of a reaction mixture of **8** and $PhI(OAc)_2$–I_2 afforded the iodolactone **10** as a diastereomeric mixture in 49% yield.[9,10a] Under identical conditions, Suárez cleavage of the epimer **9** also gave **11** (42%).

Tin hydride-mediated radical cyclizations of **10** and **11** proceeded in excellent yields, but with modest diastereoselectivities (Scheme 2).[10b,11] The relative stereochemistry of **12** was unequivocally determined by X-ray analysis; structures for the remaining products were tentatively assigned by analysis of the ^{1}H NMR spectra and consideration of the anticipated geometry of 5-*exo* cyclization.[10c] The radical cyclization of **10** thus exhibited modest diastereoselectivity in favor of the *trans*-ring fused stereochemistry, whereas no preference in the ring junction stereochemistry was observed for the mismatched cyclization of **11**. The disappointing lack of diastereocontrol in these radical cyclizations is in sharp contrast to the exclusive preference for the *trans* fused ring junction and the chair-like transition structure exhibited for a β-keto radical embedded in the unsubstituted cyclooctane ring (carried out at room temperature).[12–14] The possibility of several local conformations of similar energies for the central eight-membered ring, especially in the presence of the lactone ring and also at elevated temperatures (i.e. refluxing benzene), may account for the observed poor stereoselectivities.[14]

In summary, we have developed a facile method for the construction of a bicyclo[6.3.0]undecane skeleton by the readily available [4+3] cycloadducts, followed by sequential application of the Suárez cleavage and 5-*exo* radical cyclization. Studies are underway to achieve diastereoselective 5-*exo* cyclization by inducing a local conformational bias of the central eight-membered ring with a judicious choice of substituents and/or at low



Scheme 2.

temperatures. Also included is the application of this annulation approach to a total synthesis of natural products.

Acknowledgements

We thank the National Institutes of Health (GM 35956) for generous financial support. We are indebted to Professor Robin D. Rogers for the X-ray structure determination of **12**.

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1. Part 15 in the series of synthetic studies on [4+3] cycloadditions of oxyallyls. See also: (a) Part 14: Lee, K.; Cha, J. K. *J. Am. Chem. So*c. **2001**, *123*, 5590; (b) Part 13: Lee, J. C.; Cha, J. K. *J. Am. Chem. So*c. **2001**, *123*, 3243; (c) Part 12: Lee, J. C.; Cha, J. K. *Tetrahedron* **2000**, *56*, 10175; (d) Part 11: Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett*. **1999**, *1*, 2017.
2. For general reviews, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757; (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749; (c) Mehta, G.; Singh, V. *Chem. Rev*. **1999**, *99*, 881.
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4. For an excellent review, see: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: New York, 1996.
5. In the present study we chose to work with racemic compounds as a matter of convenience. However, we note that enzymatic asymmetrization of the *meso* diol precursor could be accomplished by the action of an appropriate lipase or esterase.[1a,3c,6]
6. Lee, K.; Cha, J. K. Unpublished results.
7. Similarly, a 16:1 mixture of the corresponding homoallyl alcohols were obtained in 81% yield from **5b**. The conspicuous difference in diastereoselectivity in the allylation reaction of **5a** and **5b** can be attributed to the bridged oxygen atom in the latter compound.
8. Deprotection of the pivaloyl group was found to greatly facilitate the separation of the two diastereomers by column chromatography.
9. (a) Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett*. **1986**, *27*, 383; (b) de Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc*. **1993**, *115*, 8865 and references cited therein; (c) See also: Ref. 3b.
10. (a) Unoptimized yield; (b) Diastereoselectivities were determined by isolation yields and/or analysis of the ^{1}H NMR spectra; (c) The products **17**–**20** were obtained as an inseparable mixture, and their stereochemistry was tentatively assigned on the basis of the ^{1}H NMR spectrum.
11. Comparable results were also obtained for the corresponding oxocanes which were prepared from **5b**.[6]
12. (a) Booker-Milburn, K. I. *Synlett* **1992**, 809; (b) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc*., *Perkin Trans. 1* **1995**, 2315.
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14. As the size of the existing ring becomes larger, an increasing amount of the *trans* ring fused products has been observed, while five- or six-membered ring systems predominantly lead to the *cis*-fused bicyclic products. See, for example: (a) Winkler, J. D.; Sridar, V. *Tetrahedron Lett*. **1988**, *29*, 6219 and references cited therein; (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem*. **1990**, *55*, 5442; (c) The orientation of the alkenyl side-chain on the existing ring, in particular cyclohexyl rings, is also known to influence the level of diastereoselectivity: RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc*. **1989**, *111*, 296.