6-endo-dig Free-Radical Carbocyclizations: A New Strategy for the Synthesis of Cyclitols

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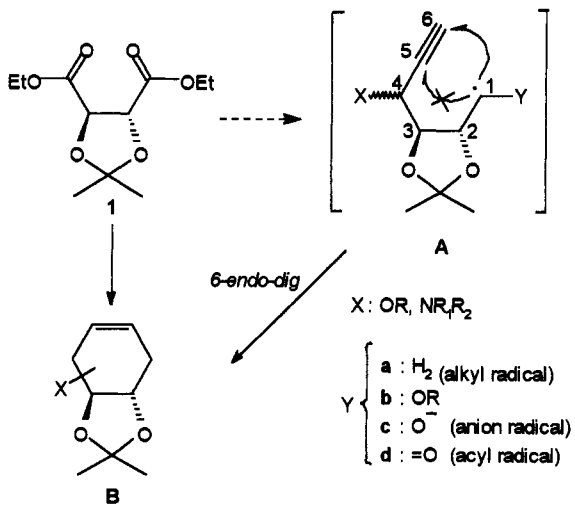
Summary: The *6-endo-dig* free radical carbocyclization of the chiral 1-iodo-5-alkynes **5** and **6** has been used to prepare the cyclitols **7–9**.

Cyclitols are polyhydroxycyclohexane derivatives with important biological activities.[1] There is currently considerable interest in the synthesis of these types of compounds.[2] We have recently described a new approach for the preparation of aminodeoxyinositols[3] and branched-chain cyclitols[4] by *6-exo-trig* radical cyclization strategies.

We now report a novel strategy for the asymmetric synthesis of inositols. This method is based in the *6-endo-dig*[5] free radical carbocyclization[6] of chiral, conveniently functionalized 1-iodo-5-alkynes.[7] We hypothesized that, as the *5-exo-dig* ring closure of intermediate **A** would be disfavored because two cyclopentanes cannot be *trans* fused, the cyclization of radical species **A** could be exclusively directed, by the *6-endo-dig* path, to the functionalized cyclohexene **B** (Scheme 1). Although kinetically controlled radical cyclizations follow preferentially the *exo* mode,[5a] major *endo* products have been observed in the ring closure with sterically hindered *exo* atoms,[5b] in the annelation of amidyl radicals with terminal bonds,[8] and when a silicon atom is involved in the radical.[9]

Scheme 1



It has been also claimed that the "*endo* ring closure is excluded for simple 5-hexynyl radicals...and when closure involves a terminal C=X bond."[10]

Contrary to these expectations we now report for the first time the successful *6-endo-dig* free-radical-promoted carbocyclization of simple 5-hexynyl radicals. We have shown that the *subtle trans located 1,3-dioxolane moiety in a radical precursor* can influence the regioselectivity in the carbon-centered cyclization. We have used this concept in the transformation of (2*R*,3*R*)-diethyl 2,3-*O*-isopropylidenetartrate **1**,[11] *via* species **Aa**[12] (Scheme 1), into cyclitols **7–9** (Scheme 2).

These ideas have been put into practice with the synthesis and cyclization of compounds **5** and **6**. The simple route **1**[11] → **2**[13] → **3**,[14] followed by Swern oxidation[15] and ethynylmagnesium bromide addition to the aldehyde **4** (Scheme 2), allowed us to obtain the radical precursor **5** in four steps and good overall yield. Compound **5** was isolated as a mixture of *anti/syn* isomers[16,17] at C4 in a

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(1) Posternak, T. *The Cyclitols*; Holden-Day: San Francisco, 1965.

(2) From sugars (Ferrier reaction): (a) Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 588. (b) Ogawa, S.; Chida, N.; Ohtuka, M.; Nakazawa, K. *J. Org. Chem.* **1991**, *56*, 2976. (c) Jaramillo, C.; Fernández de la Pradilla, R.; Martín-Lomas, M. *Carbohydr. Res.* **1991**, *209*, 296. (d) Ferrier, R. J.; Stütz, A. E. *Carbohydr.Res.* **1990**, *200*, 237. Diels–Alder strategy: Vogel, P.; Fattori, D.; Gasparini, F.; Le Drain, C. *Synlett* **1990**, 173. Microbial oxidation of arenes: (e) Carless, H. A. J.; Billinge, J. R.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 3113. (f) Ley, S. V.; Redgrave, A. J. *Synlett* **1990**, 393. (g) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077. Vinylsilane–aldehyde cyclizations: McIntosh, M. C.; Weinreib, S.M. *J. Org. Chem.* **1991**, *56*, 5010. Chemical transformations of natural inositols: Paulsen H.; Röben, M.; Heiker, F. R. *Chem.Ber.* **1981**, *114*, 3242. For related pseudo-sugars and branched-chain cyclitols: Tadano, K.-i.; Miyake, A.; Ogawa, S. *Tetrahedron* **1991**, *47*, 7259 and references cited therein. (h) Paulsen H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 125. (i) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1991**, *47*, 4571. (j) Augy-Dorey, S.; Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Sagnard, J. *J. Chem. Soc., Chem. Commun.* **1993**, 960.

(3) (a) Marco-Contelles, J.; Martínez, L.; Martínez-Grau, A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437. (b) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. See also: Redlich, H.; Sudau, W.; Szardenings, A. K.; Vollerthum, R. *Carbohydr. Res.* **1992**, *226*, 57.

(4) (a) Marco-Contelles, J.; Sánchez, B.; Pozuelo, C. *Tetrahedron: Asymmetry* **1992**, *3*, 689. (b) Marco-Contelles, J.; Sánchez, B.; Ruiz, P. *Nat. Prod. Lett.* **1992**, *1*, 167. (c) Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 4293.

(5) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(6) (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986. (c) Curran, D. P. *Synthesis* **1988**, *417*, 489. (d) Curran, D. P. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol. 4, p 779. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (f) Neumann, W. *Synthesis* **1987**, 665. (g) Motherwell, W. M.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992.

(7) For radical cyclization on a carbon triple bond in chiral templates, see: Malanda, J.-C.; Doutheau, A. *J. Carbohydr. Chem.* **1993**, *12*, 999 and ref 11 cited therein.

(8) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581 and references cited therein. (b) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.

(9) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979.

(10) Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.

(11) (a) Carmack, M.; Kelly, C. J. *J. Org. Chem.* **1968**, *33*, 2171. (b) Wiggins, L. F. *J. Chem. Soc.* **1946**, 13. (c) Fischer, E. *Chem. Ber.* **1895**, *28*, 1167.

(12) The present approach allows the preparation of epimers at C2/C3 in compounds of type **B** (Scheme 1) by using the readily available (*D*)-**1**. The different and selective manipulation of these starting materials should also provide an easy entry to other interesting radical species (**Bb–d**, Scheme 1).

(13) Feit, P. W. *J. Med. Chem.* **1964**, *7*, 14.

(14) Abushanab, E.; Bessodes, M.; Antoniakis, K. *Tetrahedron Lett.* **1984**, *25*, 3841.

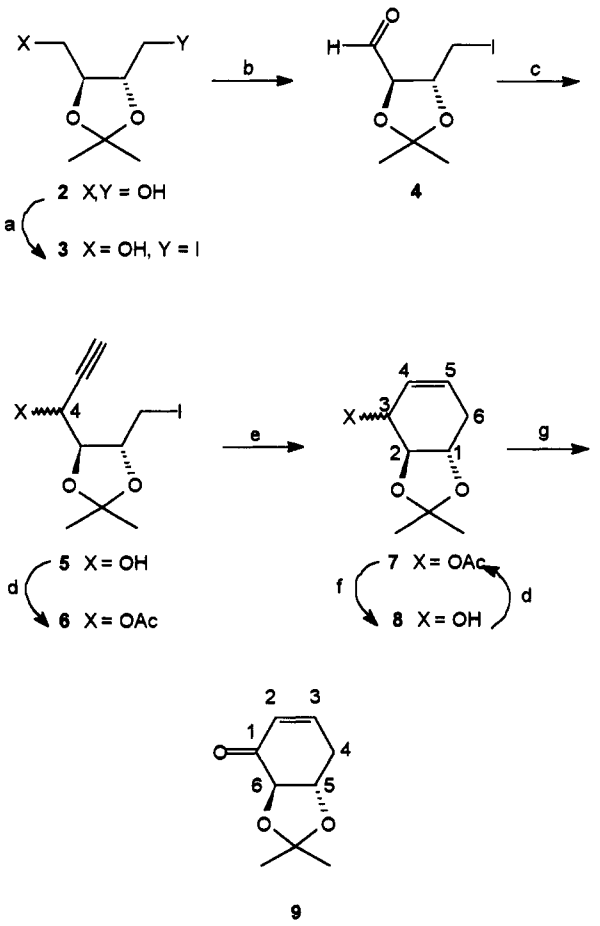
(15) Mancuso, A. J.; Huang, L.-S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(16) The presence of boron–trifluoride etherate during the addition of the Grignard reagent to compound **4** did not improve the *anti/syn* ratio.

(17) The assignment of relative configurations (*anti/syn*) in compounds **5** and **6** has been made by comparison of the chemical shifts (H4), in the ^{1}H NMR spectra, with those of analogous products obtained in the additions of acetylenic reagents to similar tartraldehyde derivatives (Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265) and have been confirmed by the analysis of spectral data of the cyclized products. Ratios of the (*anti/syn*) isomers were determined by ^{1}H NMR integration of the crude mixtures.

0022-3263/94/1959-1234$04.50/0

Scheme 2



[a] Reagents: (a) Ph_3P, I_2, imidazole, toluene (59%); (b) $(CO_2)Cl_2$, DMSO, Et_3N, CH_2Cl_2 (79%); (c) BrMgC≡CH, THF (84%); (d) Ac_2O, pyridine (90%); (e) AIBN, Bu_3SnH, toluene; (f) MeOH, Et_3N, H_2O (65%); (g) PDC, CH_2Cl_2 (70%).

63:37 ratio. This unseparable mixture was submitted to standard acetylation conditions giving a mixture of acetates **6** (*anti/syn* = 63/37) that we were also unable to separate.

With the radical precursors in hand, the cyclization was attempted.[18] The tributyltin hydride + AIBN-mediated free radical cyclization of acetate **6** (*anti* + *syn*) gave the *6-endo-dig* product **7**; after careful flash chromatography,[19] we could isolate **7**, as a mixture of isomers at C3 (*S*/*R* ≅ 1/1), and traces of the more polar isomer, pure **7** (C3 *S*), in 66% total yield. Basic hydrolysis (MeOH, Et_3N, H_2O) of compound **7** (C3 *S*) gave **8** (C3 *S*) in 88% yield. The ^1H NMR analysis of **7** (C3 *S*) and **8** (C3 *S*) unequivocally established the relative stereochemistry at C2/C3. Thus, since the molecule is in a rigid conformation, the value of $J_{2,3}$ = 3.8 Hz for $^1H_2$ in **7**(C3 *S*) suggests an axial–equatorial arrangement of protons H2 and H3. In addition, significant cross-peaks (H2/H3, H3/H6ax, H2/H6ax, and H1/H6eq) in the NOESY spectrum of **7** (C3 *S*) indicate a quasiaxial orientation of the OH group.

The cyclization of compound **5** (*anti* + *syn*), under similar conditions, and after flash chromatography,[19] afforded a mixture of isomers **8** at C3 (*S*/*R*:45/55) in 50% yield. We were unable to separate them by chromatograpy. As shown in the ^1H NMR spectrum and by comparison with the spectral data of **8** (C3 *S*), this compound was the major isomer in the mixture of epimers **8** and, as expected, corresponded to the ring closure of the major **5** (*anti*) precursor.[17]

Finally, simple acetylation or PDC oxidation[20] of the allylic alcohols **8** gave the acetates **7** (C3 *S*/*R* = 55/45; 90% yield) and the cyclohexenone **9** (70% yield), respectively. Thus, in spite of the low diastereomeric excess obtained in the formation of alcohol **5**, we could transform the corresponding cyclized isomers **8** into the homogeneous ketone **9**, a highly functionalized, chiral intermediate for the synthesis of different cyclitols and natural products.[21]

In summary, we have shown that the *6-endo-dig* cyclization of simple 5-hexynyl radicals derived from precursors **5** and **6** is feasible and the corresponding carbocycles can be obtained in good yields. This results in a new strategy for the synthesis of inositols. Work is now in progress in order to apply this methodology to other precursors and will be reported in due course.

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Supplementary Material Available: Experimental procedures for the preparation of compounds **3** and **5** and spectral data of compounds **3**, **5**, **6**, **7** (C3 *S*), **8** (C3 *S*), and **9** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) Cyclization of **5** or **6**: In a typical experiment, to a solution of the radical precursor in toluene (0.02 M), under argon and at reflux, was slowly added a solution of tributyltin hydride +AIBN (cat.) in toluene dropwise *via* syringe pump over 7 h. The mixture was cooled and the solvent evaporated. The residue was dissolved in ether and treated with an aqueous solution (20%) of potassium fluoride. After the mixture was stirred overnight, the organic phase was separated, dried, evaporated, and submitted to chromatography, eluting with hexane/ethyl acetate mixtures. Ratios of the purified cyclization compounds determined by ^1H NMR integration were similar to the values determined in crude mixtures.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(20) (a) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (b) Herscovici, J.; Antoniakis, A. *J. Chem. Soc., Chem. Commun.* **1980**, 561.

(21) (1*S*,2*R*,3*S*)-2,3-*O*-Isopropylidenecyclohex-4-ene-1,2,3-triol, an isomer of compound **8** (C3 *S*), has been recently synthesized and transformed into pseudosugars (Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 245. See also: Maycock, C. D.; Barros, M. T.; Santos, A. G.; Godinho, L. S. *Tetrahedron Lett.* **1992**, *33*, 1633). In addition, the C1/C3 epimer of compound **8** (C3 *S*) has also been prepared in enantiomerically pure form by enzymatic resolution and transformed into the C5 epimer of product **9**; this ketone is the key intermediate in the total synthesis of (+)-palitantin (Deruythere, X.; Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 51).