6-Exo Free Radical Cyclization of Acyclic Carbohydrate Intermediates: A New Synthetic Route to Enantiomerically Pure Polyhydroxylated Cyclohexane Derivatives

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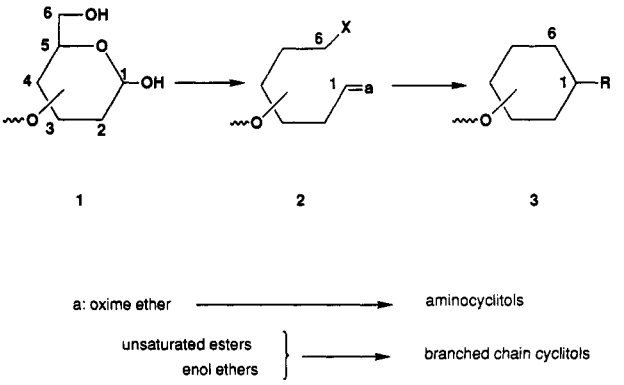
The 6-exo free radical cyclization of conveniently functionalized acyclic carbohydrate derivatives is a new and efficient method for the asymmetric synthesis of polyhydroxylated cyclohexane compounds (aminocyclitols, pseudosugars). The scope and versatility of this synthetic route has been analyzed by changing the absolute configuration of the radical precursors and the nature of the radical trap. The yield and stereoselectivity in this process is very structure dependent.

Introduction

Cyclitols are polyhydroxylated cyclohexanes formally related to the simple carbohydrates.[1] The aminocyclitols[2] and the branched chain cyclitols (pseudosugars)[3] are subclasses of cyclitols with important biological activities; the aminocyclitols form the aglycon part of numerous aminoglycoside antibiotics, e.g., streptomycin and fortimycin;[4] the branched chain cyclitols have shown specific inhibition for glycosidases[5] and potential use as artificial sweeteners.[6] Despite many synthetic efforts,[7] the synthesis of enantiomerically pure polyhydroxylated cyclohexane derivatives remains a challenge. New methods are sought in order to provide efficient synthetic routes to these compounds. In most of these approaches sugars have been used as chiral starting materials. In fact, the synthesis of carbocycles from carbohydrates has been an area of interest and growing activity in the last decade.[8] A number of strategies have been developed in order to fulfil this objective.[7,9] In this context, free radical cyclization[10] of sugar derivatives has proven to be an elegant and efficient method for the synthesis of complex and polyfunctionalized carbocycles.[11] Wilcox[12] was the first to carry out such cyclization with unsaturated acyclic halo sugars. A subsequent study reported by Bartlett[13] has established the potential of oxime ethers as acceptors in these processes.

Scheme I



Results and Discussion

In this paper[14] we report the preparation of some chiral amino and branched chain cyclitol derivatives via a new synthetic route to polyhydroxylated cyclohexane derivatives. The strategy is shown in Scheme I and is based on *6-exo*[15] *free radical cyclization of acyclic and conveniently functionalized sugar intermediates* **2** derived from readily available compounds **1**. Fraser-Reid[16] has reported a

(1) Anderson, L. In *The Carbohydrates. Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. Ia, Chapter 15.
(2) Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111.
(3) Ogawa, S. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 26.
(4) Hooper, R. In *Aminoglycoside Antibiotics*; Umezawa, H., Hooper, I. R., Eds.; Springer, Berlin, **1981**; p 7.
(5) Miwa, I.; Hava, H.; Okuda, J.; Suami, T.; Ogawa, S. *Biochem. Int.* **1985**, *11*, 809.
(6) Ogawa, S.; Uematsu, Y.; Yoshida, S.; Sesaki, N.; Suami, T. *J. Carbohydr. Chem.* **1987**, *6*, 471.
(7) Aminocyclitols. Suami, T.; Ogawa, S.; Tauno, N.; Saguro, M.; Rinehart, K. L. *J. Am. Chem. Soc.* **1976**, *98*, 7110. Semeira, D.; Philippe, M.; Delaumeny, J. M.; Sepulchre, A. M.; Gero, S. D. *Synthesis* **1983**, 710. Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.* **1983**, *48*, 4786. Kuo, C. H.; Wendler, N. L. *Tetrahedron Lett.* **1985**, *25*, 2291. Beier, B.; Schürrle, K.; Werbitzky, O.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2255. Paulsen, H.; Röben, W.; Heiker, F. R. *Chem. Ber.* **1981**, *114*, 3242. Schubert, J.; Schwesinger, K.; Knothe, L.; Prinzbach, H. *Liebigs Ann. Chem.* **1986**, 2009. Baer, H. H.; Arai, I.; Radatus, B.; Rodwell, J.; Chinh, N. *Can J. Chem.* **1987**, *65*, 1443. Ferrier, R.; Stütz, A. E. *Carbohydr. Res.* **1990**, *200*, 237. Shing, T, K. M.; Elsley, D. A.; Gilehouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171. Branched Chain Cyclitols. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171. Barton, D. H. R.; Gero, S. D.; Cleophax, J.; Machado, D. S.; Quiclet-Sire, B. *J. Chem. Soc., Chem. Commun.* **1988**, 1184. Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1008. Köhn, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1987**, 1045. Ogawa, S.; Orihara, M. *Carbohydr. Res.* **1988**, *177*, 199. Paulsen, H.; Deyn, W. *Liebigs Ann. Chem.*, **1987**, 125. Tadano, K.; Maeda, H.; Hoshino, M.; Yimura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946. Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 748. Barton, D. H. R.; Dalko, P.; Gero, S. D. *Tetrahedron Lett.* **1991**, *32*, 2471.
(8) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: Oxford, 1983.
(9) Fraser-Reid, B.; Tsang, R. *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, p 123.
(10) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bond*; Pergamon: Oxford, 1986.
(11) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. Rajan-Babu, T. V. *J. Org. Chem.* **1988**, *53*, 4522. RajanBabu, T. V.; Fukunaga, T. *Ibid.* **1989**, *111*, 296. Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1990**, *112*, 4374. Othman, A. A.; Matadi, N. A.; Timari, H. S. *J. Antibiot.* **1978**, *31*, 1007. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. Dickson, J. K.; Tsang, R.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5350. Yeung, B. W. A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160. Vité, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2271.
(12) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546.
(13) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.
(14) Part of this work has been the subject of a preliminary communication: Marco-Contelles, J.; Martinez, L.; Pozuelo, C.; Martinez-Grau, A.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437.
(15) A relatively reduced examples of 6-exo free radical cyclizations have been described: Batty, D.; Crich, D.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1366 and references cited therein.
(16) Yeung, B. W. A.; Alonso, R.; Vité, G. D.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1989**, *8*, 413.

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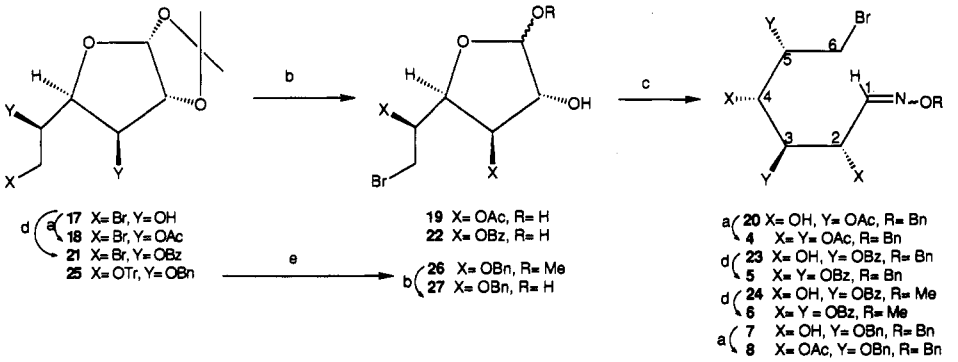
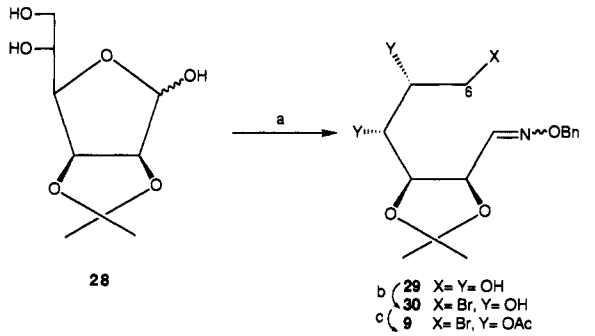
Scheme II[a]



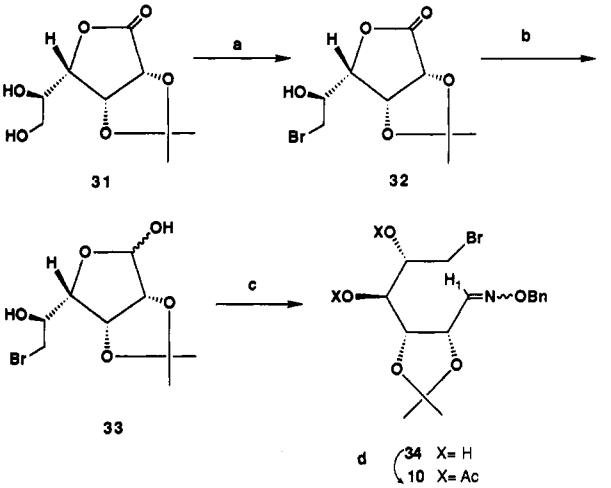
[a] Key: (a) Ac_2O, pyridine (54%); (b) CF_3CO_2H, H_2O (9:1) (88%); (c) $BnONH_3Cl$ or $MeONH_3Cl$, pyridine, CH_2Cl_2, H_2O (95%); (d) BzCl, pyridine (81%); (e) 4% H_2SO_4, MeOH (73%), then CBr_4, Ph_3P (60%).

Scheme III[a]



[a] Key: (a) $BnONH_3Cl$, pyridine (63%); (b) CBr_4, Ph_3P (60%); (c) Ac_2O, pyridine (85%).

Scheme IV[a]



[a] Key: (a) CBr_4, Ph_3P (45%); (b) DIBAH, toluene, −78 °C (66%); (c) $BnONH_3Cl$, pyridine, CH_2Cl_2, H_2O (50%); (d) Ac_2O, pyridine (75%).

partial success in the free radical cyclization of substrates related to **2**, with aldehydes as acceptors. If this strategy could be executed in practice we would have in hand a new and powerful method for the preparation of advanced chiral intermediates for the synthesis of natural or modified aminocyclitols and pseudosugars.

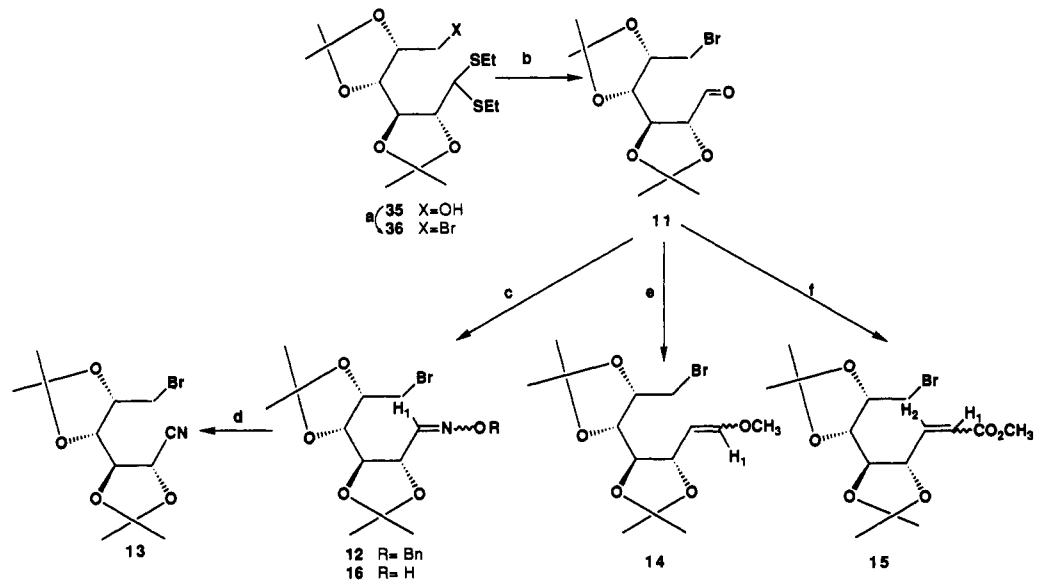
With this scenario in mind we have synthesized a range of different radical precursors, thereby allowing a thorough and balanced assessment of this approach. So, we have prepared the *gluco* type derivatives **4–8** and **11–15**, with different protecting groups at carbons C2–C5 (sugar numbering) and radical traps at C1. In addition, we have prepared the *manno* **9** and *gulo* **10** derivatives.

The radical precursors **4–15** have been obtained by routine methods (see supplementary material). Compounds **4–6** have been synthesized from 6-bromo-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**17**)[17] (Scheme II) by total acetylation (Ac_2O/pyridine, rt, 24 h) or benzoylation (BzCl/pyridine, rt, 24 h), acid hydrolysis (CF_3COOH/H_2O, 9:1), and oxime ether formation ($BnONH_3Cl$ or $MeONH_3Cl$/pyridine, methylene chloride, water, reflux, 18 h) of the resulting compound, followed by complete acetylation or benzoylation. Compound **7** could be prepared from 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-trityl-α-D-glucofuranose (**25**)[18] (Scheme II) by total acid hydrolysis (4% H_2SO_4/methanol), bromination (CBr_4, Ph_3P), and acid hydrolysis (CF_3COOH/H_2O, 9:1) of the resulting compound **26** followed by oxime ether formation. Acetylation of compound **7**, under standard conditions, gave the precursor **8**. The *manno* precursor **9** has been obtained from 2,3-*O*-isopropylidene-α-D-mannofuranose (**28**)[19] (Scheme III) by first oxime ether formation, bromination at C6, and acetylation. Compound **10** (*gulo* type) has been prepared from 2,3-*O*-isopropylidene-D-gulonolactone (**31**)[20] (Scheme IV) by selective bromination and reduction (DIBAH, toluene, −78 °C) of the resulting compound followed by oxime ether formation and acetylation. The *gluco* derivative **11** was synthesized from the alcohol **35**[21] (Scheme V) by bromination and deprotection of the aldehyde (HgO, $HgCl_2$, acetone, water, 60 °C). Oximes **12** and **16** have been obtained from aldehyde **11**, following the standard method. Nitrile **13** has been obtained from oxime **16** by dehydration (trifluoroacetic anhydride, pyridine). Compounds **14** and **15** resulted from Wittig reactions of the corresponding ylides with the aldehyde **11**. In general, these radical precursors have been synthesized in moderate to good yield in multigram quantities. All new compounds showed good analytical and spectroscopic data (see supplementary material).

Compounds **4–10** and **12** have been obtained as mixtures of syn and anti isomers in a 70:30 ratio, respectively, as

(17) Whistler, R. L.; Anisuzzaman, D. K. M. *Methods in Carbohydrate Chem.* **1980**, *8*, 227.
(18) Dax, K.; Wolflehner, W.; Weidmann, H. *Carbohydr. Res.* **1978**, *65*, 132.
(19) Freudenberg, K.; Wolf, A. *Chem. Ber.* **1927**, *60*, 1232.
(20) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.
(21) Wong, M. J. H.; Gray, G. R. *Carbohydr. Res.* **1980**, *80*, 87.

Scheme V[a]



[a] Key: (a) CBr_4, Ph_3P (70%); (b) HgO, $HgCl_2$, acetone, H_2O (80%); (c) $BnONH_3Cl$ or $HONH_3Cl$, pyridine, CH_2Cl_2, H_2O (76%); (d) $(CF_3CO)_2O$, pyridine (90%); (e) $Ph_3P{=}CHOCH_3$, THF, -20 °C (50%); (f) $Ph_3P{=}CHCO_2CH_3$, toluene (85%).

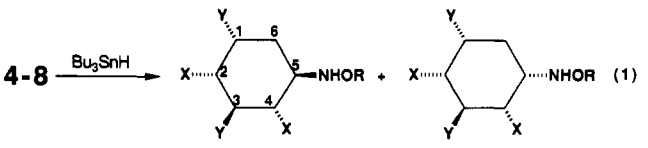
Table I. Tin Hydride Cyclization of Oxime Ethers

entry	substrate no.	X	Y	R	product ratio[a] 37/38	yield (%)[b]
1	4	OAc	OAc	Bn	83/17	52
2	5	OBz	OBz	Bn	75/25	55
3	6	OBz	OBz	Me	73/27	50
4	7	OH	OBn	Bn	80/20	40
5	8	OAc	OBn	Bn	78/22	42

[a] Product ratios from ^1H NMR analysis of crude mixture. [b] Total yield of the cyclized product after chromatography.

we could determine by ^1H NMR analysis (syn δ H1 7.30, d, J = 7.3 Hz; anti δ H1 6.80, d, J = 5.5 Hz). The enol ether **14** has been obtained as a mixture of E/Z 1/1 isomers (E: δ H1 6.62, d, J = 12 Hz; Z: δ H1 6.12, d, J = 6 Hz). The α,β-unsaturated ester **15** has been obtained as a mixture of E/Z 1/1 isomers when the Wittig reaction was conducted in toluene or methylene chloride (E: δ H1 6.19, dd, J = 1.4 and 15.6 Hz; Z: δ H1 6.00, dd, J = 1.1 and 11.7 Hz); when methanol was used as solvent[22] the ratio E/Z was 1/7. It is important to point out that we were unable to separate the isomers in compounds **4–8**, **9**, **10**, **12**, **14**, and **15** by the conventional chromatographic techniques.

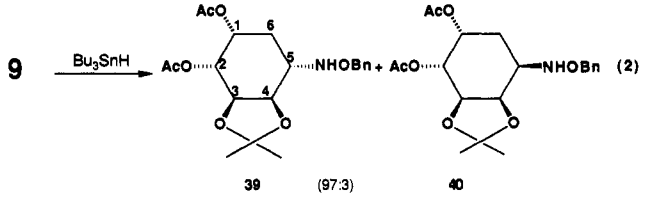
The tributyltin hydride mediated free radical cyclization of these unseparable mixtures of isomers has been performed (see Experimental Section) under high dilution in toluene (0.015 M), using dropwise addition (syringe pump). Under these conditions the *gluco* derivatives **4–8** gave the expected aminocyclitols **37/38** (eq 1) in yields and product



37 **38**

ratios shown in Table I. The ^1H NMR analysis of the crude mixtures showed a 4:1 ratio of isomers in the reaction products; these values are independent of the nature of the substituent at C5 in the radical precursor. In some instances (entries 1 and 3) we could isolate pure, after chromatography and recrystallization, the major isomer **37**. For compounds **5**, **7**, and **8**, the purification of the major isomers was troublesome and we have obtained the corresponding carbocycles as oils that we could not recrystallize in 60%, 92%, and 78% maximum diastereomeric excesses, respectively. The total yield of the isolated carbocycles has been only moderate (50%); this is probably due to the formation of some polar compounds, incompletely identified. Several changes in the reaction conditions, using 1.2 equiv of tributyltin hydride or a higher dilution (0.01 M) or benzene as solvent, did not affect the yield. In these type of compounds we have never observed the formation of the reduced starting material. The absolute configuration at the new stereocenter in compounds **37** has been established by careful ^1H NMR analysis and selective proton–proton decoupling experiments. In the major isomers, H5 has been easily identified, appearing at δ 3.15–3.63, ddd, with vicinal coupling constants ($J_{4,5}$ = 10 Hz, $J_{5,6(ax)}$ = 12.5 Hz, $J_{5,6(eq)}$ = 4.2 Hz) in good agreement with 5*R* as absolute configuration for a cyclohexane ring in a chair-like conformation.

Encouraged by these promising results we next tried the free radical cyclization of compound **9**. Under the usual conditions this *manno*-type derivative gave a mixture of compounds **39/40** in a 97:3 ratio as we could determine by ^1H NMR in the crude reaction (eq 2). After chroma-

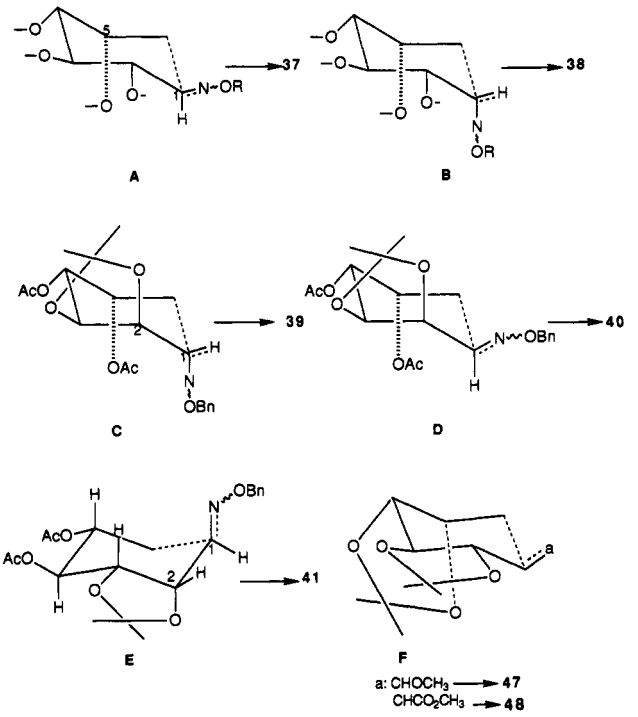


39 (97:3) **40**

tography we isolated the pure major isomer **39** in 50% yield. The absolute stereochemistry at the new stereocenter in this compound has been established by careful ^1H NMR analysis; we have observed δ H6(eq) 2.16 (dt, $J_{6(eq),1} = J_{6(eq),5}$ = 5.4 Hz; $J_{6(eq),6(ax)}$ = 13.6 Hz), δ H6(ax) 1.90 (ddd, $J_{5,6(ax)}$ = 9.8 Hz; $J_{1,6(ax)}$ = 8.0 Hz; $J_{6(eq),6(ax)}$ = 13.6 Hz). H5 appears at 3.19 ppm as a multiplet showing a

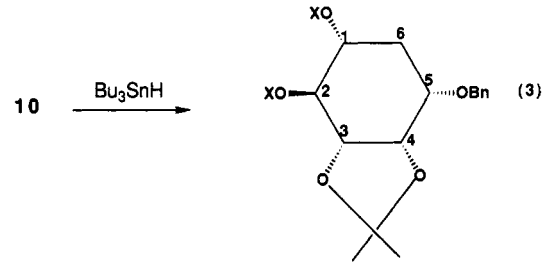
(22) Valverde, S.; Martin-Lomas, M.; Herradón, B.; García-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895.

Scheme VI



vicinal coupling constant $J_{4(ax),5(ax)}$ = 6.7 Hz, which is consistent with the assigned absolute configuration at C5 (*S*) being the carbocycle in a chair-like conformation.

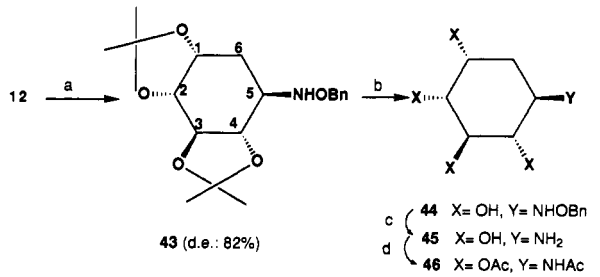
The radical precursor **10** (*gulo* type), under the usual free radical conditions, gave only the expected carbocycle **41** (eq 3), isolated after chromatography in 50% yield. The



absolute configuration at the new stereocenter C5 (*R*) has been determined by ^{1}H NMR analysis and selective proton–proton decoupling experiments; we could observe δ H5 3.53 as a multiplet and coupling constants $J_{4,5}$ = 3.7 Hz, $J_{5,6(ax)} = J_{5,6(eq)}$ = 4.6 Hz, $J_{1,2}$ = 9.2 Hz, $J_{1,6(eq)}$ = 5.3 Hz, $J_{1,6(ax)}$ = 8.8 Hz, coherent with *R* as absolute configuration for a cyclohexane in a chair conformation; an alternaive *S* as absolute configuration for a cyclohexane in a boat conformation, also consistent with the ^{1}H NMR data, was finally discarded in view of the fact that no NOE effect was observed between H4 and 2-H6. Basic hydrolysis gave the partially deprotected aminocyclitol **42** (eq 3) whose spectroscopic data are also in good agreement with this structure.

In Scheme VI we present a simple model that could justify the stereochemical outcome of the free radical cyclization of compounds **4–10**. It is important to point out that the final result is the sum of the combined effects in the syn + anti isomers; unfortunately, we could not separate them and consequently analyze independently their cyclization. This can be applied to the other cases analyzed here (see below). In spite of this, and analyzing the results obtained in the cyclization of compounds **4–8** (see Table I), we can conclude that in the chair-like conformations **A** and **B**, corresponding to the transition states leading to the carbocycles **37–38** (Scheme VI), the steric repulsion between the substituent at C5 and C1 is not critical. We can assume that, as in the hex-5-enyl radical cyclization, the major products arise via conformers where the substituents occupy quasiequatorial positions.[23] The observed improvement on going to substrates **9** and **10** point to the significance of the gauche interaction between the C2 substituent (isopropylidenedioxy group) and the C1 substituent (alkyl oxime ether) (see structures **C** and **E**; Scheme VI).

Scheme VII[a]



[a] Key: (a) Bn_3SnH, AIBN, toluene (75%); (b) $AcOH/H_2O$ (7:3) (70%); (c) H_2, Pd/C, MeOH, 1 atm; (d) Ac_2O, pyridine [44 → 46, (59%)].

At this point it was clear that the type of functionalization in the radical precursor had a powerful influence in the stereochemical course of the process; the yields of the cyclized products were only moderate and it was of interest to prove other radical traps in order to extend the versatility of the method. So, we have designed and synthesized the radical precursors **14** and **15** (*gluco* type) derived from the readily available aldehyde **11**; in this compounds the oxygens at C2–C5 are blocked as isopropylidenedioxy groups, giving the desired rigidity. Not surprisingly these expectations have been confirmed; we have obtained better diastereomeric excesses and chemical yields.

The free radical cyclization of the oxime ether **12**, under typical conditions (see Experimental Section), gave the major carbocycle **43** (Scheme VII) in high diastereomeric excess (de 82%) and good yield (75%). The absolute configuration at C5 (*R*) (δ H5 3.40–3.20, m) was firmly established after ^{1}H NMR analysis; in effect, we could observe vicinal coupling constants $J_{6(eq),5}$ = 4.8 Hz, $J_{6(ax),5}$ = 9.0 Hz consistent with previous observations (see above; compounds **37**/**38**) for a cyclohexane in a chair-like conformation. Compound **43** has been submitted to further transformation: acid hydrolysis gave the tetrol **44** that, after hydrogenation, afforded the amino alcohol **45**; this compound has been characterized as its peracetate **46** (Scheme VII).

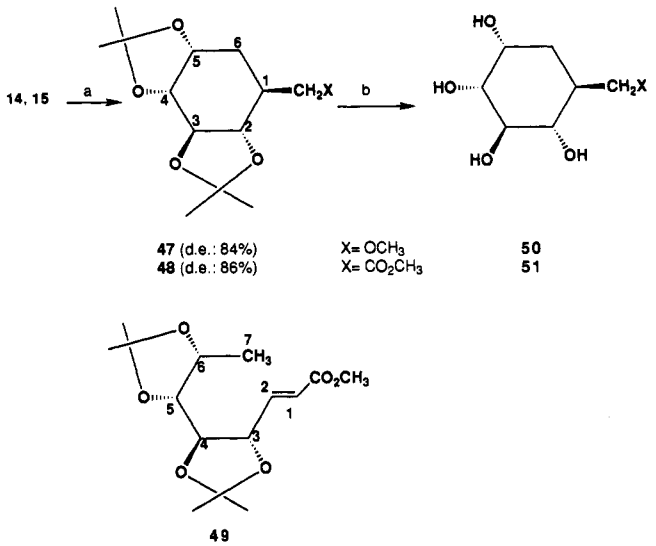
The good result obtained in the cyclization of compound **12** prompted us to study the free radical cyclization of the aldehyde **11** and nitrile **13**. Unfortunately we could not detect the expected carbocycles from these substrates. This is in accord with other previous reports[16,24] about the low ability of these functional groups as radical acceptors.

On the contrary, the enol ether **14** (*E*/*Z* 1/1) submitted to 6-exo cyclization gave the carbocycle **47** (Scheme VIII)

(23) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. Beckwith, A. L. J.; Easton, J. C.; Lawrence, T.; Serelis, A. K. *Austr. J. Chem.* **1983**, *36*, 545. Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. *Can. J. Chem.* **1987**, *65*, 1859.

(24) Esch, P. M.; Hiemstra, H.; Speckamp, N. N. *Tetrahedron Lett.* **1990**, *31*, 759.

Scheme VIII[a]



[a] Key: (a) Bu_3SnH, AIBN, toluene [14 → 47 (60%); 15 → 48 (80%)]; (b) $AcOH/H_2O$ 7:3, [47 → 50 (70%); 48 → 51 (68%)].

(de in crude mixture: 84%). The α,β-unsaturated ester **15** (E/Z 1/1) afforded, in the same conditions, compound **48** (Scheme VII) (de in crude mixture: 86%) plus the reduced and uncyclized product **49** (7% yield). In each case, simple chromatography and recrystallization gave pure the major isomers **47** [C1(*S*)] and **48** [C1(*S*)] in 60% and 80% yields, respectively; the minor carbocyclic isomers could not be obtained pure during the chromatography and were recovered partially contaminated with the major isomers (this applies also for the cyclization of compound **12**).

The formation of compound **49** [^{1}H NMR: δ 6.90 (dd, $J_{2,3}$ = 4.0 Hz, $J_{1,2}$ = 15.8 Hz, 1 H, H2), 6.15 (dd, $J_{1,2}$ = 15.8 Hz, $J_{1,3}$ = 2.0 Hz, 1 H, H1), 1.28 (d, J = 5.9 Hz, 3 H, CH_3)] during the free radical cyclization of the α,β-unsaturated **15** is noteworthy, because this is the first case in the present study where we have detected a reduced starting material, but in very low yield.

We have also cyclized the radical precursor **15**, as a mixture of E/Z isomers in 1:7 ratio and observed that the stereochemical result is the same and independent of the ratio of the isomers in the substrate **15**. This has also been observed by RajanBabu in related compounds during 5-exo free radical cyclizations.[25]

The absolute configuration at C1 in compound **47** and **48** has been established as *S* by ^{1}H NMR analysis; we have observed for H7 vicinal coupling constants $J_{1,2}$ = 9.7 Hz, $J_{6(ax),1}$ = 10.6 Hz, $J_{6(eq),1}$ = 5.1 Hz; compound **48** shows a similar pattern in the ^{1}H NMR spectrum.

Finally, acid hydrolysis of the branched chain cyclitols **47** and **48** gave the full deprotected compounds **50** and **51**.

The stereochemical results obtained in the cyclization of compounds **12**, **14**, and **15** can be rationalized by invoking the model previously discussed (Scheme VI structure **F**); the acceptor is prone to be in a pseudoequatorial position[23] that gives the major products.

In summary, in this work we have developed a new synthetic route for the chiral synthesis of polyhydroxycyclohexane compounds based on 6-exo free radical cyclization of acyclic carbohydrate derivatives. A range of radical precursors have been synthesized and cyclized, showing the scope and versatility of the method.

(25) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

Experimental Section

General Procedures. Melting points were determined in a Kofler apparatus and are uncorrected. The ^{1}H NMR coupling constants were verified by homonuclear decoupling experiments. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2-mm layers) containing a fluorescent indicator (Merck, 5539). Detection was by UV (254 nm), followed by charring with sulfuric acid spray, or with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g), and cerium sulfate hydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed by using Kiesegel 60 (230–400 mesh, Merck) silica gel and hexane/ethyl acetate mixtures as eluent.

Standard Procedure for Free Radical Cyclization. The bromide in dry toluene (0.015 M), at reflux, under argon was treated with tributyltin hydride (2.4 equiv) and AIBN (cat.) by dropwise addition (syringe pump). The reaction mixture was cooled and the solvent evaporated. The residue was dissolved in ether and 10% aqueous potassium fluoride solution was added, and the mixture stirred for 18 h. The organic phase was separated, dried, and evaporated. Flash chromatography[26] of the residue gave the product.

Free Radical Cyclization of 4. Compound **4** (1.3 g, 2.5 mmol) was cyclized by following the general procedure. The hydride was added in 2 h. After chromatography (hexane/EtOAc, 4:1) we obtained (**37**/**38**)**a** (570 mg, 52%). Recrystallization from hexane gave pure **37a** (the minor isomer **38a** was detected impurified with **37a**, in the mother liquors). **37a**: mp 116–118 °C; $[\alpha]^{25}_D$ −72° (*c* 4.5, $CHCl_3$); IR (KBr) 3200, 3080, 1755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5 H, aromatic), 5.44 (q, J = 3.1 Hz, 1 H, H1), 5.35 (t, J = 10 Hz, 1 H, H3), 5.21 (t, J = 10 Hz, 1 H, H4), 4.92 (dd, J = 10 and 3.2 Hz, 1 H, H2), 4.61 (s, 2 H, $NHOCH_2C_6H_5$), 3.25 (ddd, J = 10.1, 12.4, and 4.2 Hz, 1 H, H5), 2.10, 2.03, 2.01, 1.98 (s, s, s, s, $OCOCH_3$), 1.88 (ddd, J = 3.0, 12.4, and 14.8 Hz, H6(ax)); ^{13}C NMR (20 MHz, $CDCl_3$) δ 170.23, 170.05, 169.97, 169.91 ($OCOCH_3$), 139.14, 128.67, 128.55, 128.14 (aromatic), 76.99 (OCH_2C_{6H5}), 71.87, 71.72, 71.20, 67.82 (C1, C2, C3, C4), 56.87 (C5), 29.78 (C6), 21.01, 20.84, 20.75, 20.66 ($OCOCH_3$); MS *m*/*z* 438 (M^+ + 1, 8). Anal. Calcd for $C_{21}H_{27}NO_9$: C, 57.66; H, 6.17; N, 3.20. Found: C, 57.27; H, 6.12; N, 3.50.

Free Radical Cyclization of 5. Compound **5** (628 mg, 0.82 mmol) was transformed by the standard procedure. The hydride was added in 5 h. Flash chromatography (hexane/EtOAc, 4:1) gave compound (**37**/**38**)**b** (317 mg, 55%) as an unseparable mixture of isomers; in the collected fractions the best ratio (**37**/**38**)**b** was 80/20 (de 60%): oil; IR (film) 3500, 3060, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (major isomer) 7.60–7.25 (m, 25 H, aromatic), 6.15 (t, $J_{2,3}$ = $J_{3,4}$ = 10.3 Hz, 1 H, H3), 5.91 (ddd, $J_{1,6(eq)}$ = 4.1 Hz, $J_{1,6(ax)}$ = 2.5 Hz, $J_{1,2}$ = 3.2 Hz, 1 H, H1), 5.82 (t, $J_{4,5}$ = $J_{3,4}$ = 10.3 Hz, 1 H, H4), 5.51 (dd, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, H2), 4.62 (s, 2 H, $NHOCH_2C_6H_5$), 3.63 (ddd, $J_{4,5}$ = 10.3 Hz, $J_{5,6(ax)}$ = 12.5 Hz, $J_{5,6(eq)}$ = 4.1 Hz, 1 H, H5), 2.52 (dt, 1 H, $J_{6(eq),6(ax)}$ = 14.9 Hz, H6(eq)), 2.22 (ddd, 1 H, H6(ax)). Anal. Calcd for $C_{41}H_{35}NO_9$: C, 71.82; H, 5.11; N, 2.04. Found: C, 71.58; H, 5.40; N, 2.31.

Free Radical Cyclization of 6. Compound **6** (900 mg, 1.3 mmol) was cyclized by following the general method. The hydride was added in 5 h. After chromatography (hexane/EtOAc, 4:1) we obtained (**37**/**38**)**c** (267 mg) and **37c** (139 mg) (total yield 50%). **37c**: mp 71–73 °C; $[\alpha]^{25}_D$ −105° (*c* 0.7, $CHCl_3$); IR (KBr) 3420, 3070, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.20 (m, 20 H, aromatic), 6.19 (t, $J_{2,3}$ = $J_{3,4}$ = 10.3 Hz, 1 H, H3), 5.95 (ddd, $J_{1,2}$ = 3.1 Hz, $J_{1,6(eq)}$ = 4.0 Hz, $J_{1,6(ax)}$ = 2.4 Hz, 1 H, H1), 5.81 (t, $J_{4,5}$ = $J_{3,4}$ = 10.3 Hz, 1 H, H4), 5.53 (dd, $J_{1,2}$ = 3.1 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, H2), 3.63 (ddd, $J_{4,5}$ = 10.3 Hz, $J_{5,6(ax)}$ = 12.5 Hz, $J_{5,6(eq)}$ = 4.2 Hz, 1 H, H5), 3.48 (s, $NHOCH_3$), 2.59 (dt, 1 H, $J_{6(eq),6(ax)}$ = 14.8 Hz, H6(eq)), 2.27 (ddd, 1 H, H6(ax)). Anal. Calcd for $C_{35}H_{31}NO_9$: C, 68.96; H, 5.09; N, 2.29. Found: C, 68.98; H, 5.30; N, 2.50.

Free Radical Cyclization of 7. Compound **7** (660 mg, 1.2 mmol) was treated according to the standard method. The hydride was added in 4 h. Chromatography (hexane/EtOAc, 7:3)

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

gave (37/38)d (196 mg, 40% yield) as a mixture of isomers that we could not separate by flash chromatography; in the collected fraction the best ratio of isomers was 94/6 (de 92%): oil; IR (film) 3450, 3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 7.40–7.27 (m, 15 H, aromatic), 4.93 (d, J = 11.4 Hz, 1 H, $OCH_2C_6H_5$), 4.74 (d, J = 10.3 Hz, 1 H, $OCH_2C_6H_5$), 4.68 (d, J = 11.4 Hz, 1 H, $OCH_2C_6H_5$), 4.47 (d, J = 10.3 Hz, 1 H, $OCH_2C_6H_5$), 4.08 (s, 2 H, $NHOCH_2C_6H_5$), 3.88 (m, 1 H, H1), 3.62–3.58 (m, 3 H, H2, H3, H4), 3.10 (ddd, $J_{4,5}$ = 8.5 Hz, $J_{5,6(eq)}$ = 3.8 Hz, $J_{5,6(ax)}$ = 13.4 Hz, 1 H, H5), 2.28 (dt, $J_{6(eq),1}$ = 3.8 Hz, $J_{6(eq),6(ax)}$ = 14.2 Hz, 1 H, H6(eq)), 1.51 (ddd, $J_{6(ax),1}$ = 2.3 Hz, 1 H, H6(ax)). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 71.99; H, 6.90; N, 3.05.

Free Radical Cyclization of 8. Compound 8 (1.0 g, 1.6 mmol) was transformed by following the usual method. The hydride was added in 4 h. Chromatography (hexane/EtOAc, 4:1) gave product (37/38)e (367 mg, 42% total yield) as a mixture of isomers that we could not separate by chromatography; in the collected fractions the best ratio was 89/11 (de 78%): oil; IR (film) 3400, 3080, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 7.35–7.15 (m, 15 H, aromatic), 5.10 (t, $J_{4,3} = J_{4,5}$ = 10 Hz, 1 H, H4), 4.75 (dd, J = 3.0 and 9.1 Hz, 1 H, H2), 4.62 (d, J = 11.8 Hz, 1 H, $OCH2C_6H_5$), 4.57 (s, $NHOCH_2C_6H_5$), 4.53 (d, J = 11.8 Hz, 1 H, $OCH_2C_6H_5$), 4.52 (d, J = 12.2 Hz, 1 H, $OCH_2C_6H_5$), 4.42 (d, J = 12.2 Hz, 1 H, $OCH_2C_6H_5$), 3.93 (t, J = 10.0 Hz, 1 H, H3), 3.89 (m, 1 H, H5), 3.21 (ddd, J = 4.4, 13.0, and 10.2 Hz, 1 H, H5), 2.16 (dt, J = 4.2 and 14.4 Hz, 1 H, H6(eq)), 1.91, 1.88 (s, s, $OCOCH_3$), 1.55 (ddd, J = 2.2, 14.4, and 10.2 Hz, 1 H, H6(ax)). Anal. Calcd for $C_{31}H_{35}NO_7$: C, 69.77; H, 6.61; N, 2.63. Found: C, 69.41; H, 6.52; N, 2.31.

Free Radical Cyclization of 9. Compound 9 (322 mg, 0.68 mmol) was cyclized according to the standard method. The hydride was added in 3 h. After flash chromatography (hexane/EtOAc, 7:3) we obtained compound 39 (154 mg, 50%) as an oil: $[\alpha]^{25}_D$ +2.7° (c 2.2 $CHCl_3$); IR (film) 3500, 3080, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5 H, aromatic), 5.30–5.20 (m, 2 H, H1, H2), 4.70 (s, 2 H, $OCH_2C_6H_5$), 4.22 (m, 2 H, H3, H4), 3.19 (m, 1 H, H5), 2.16 (dt, $J_{1,6(eq)} = J_{5,6(eq)}$ = 5.4 Hz, $J_{6(eq),6(ax)}$ = 13.6 Hz, 1 H, H6(eq)), 2.08, 2.01 (s, s, $OCOCH_3$), 1.90 (ddd, $J_{6(ax),5}$ = 9.8 Hz, $J_{6(ax),1}$ = 8.0 Hz, 1 H, H6(ax)), 1.46, 1.33 (s, s, $OC(CH_3)_2O$). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.92; N, 3.56. Found: C, 60.85; H, 6.83; N, 3.71.

Free Radical Cyclization of 10. Compound 10 (1.51 g, 3.2 mmol) was cyclized by following the standard procedure. The hydride was added in 5 h. After flash chromatography (hexane/EtOAc, 4:1) we obtained compound 41 (628 mg, 50%) as an oil: $[\alpha]^{25}_D$ +45° (c 1.9, $CHCl_3$); IR (film) 3490, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, aromatic), 5.18 (dd, $J_{1,2}$ = 9.2 Hz, $J_{2,3}$ = 7.1 Hz, 1 H, H2), 5.05 (td, $J_{1,6(ax)}$ = 8.8 Hz, $J_{1,6(eq)}$ = 5.3 Hz, $J_{1,2}$ = 9.2 Hz, 1 H, H1), 4.75 (d, J = 11.7 Hz, 1 H, $NHOCH_2C_6H_5$), 4.70 (d, J = 11.7 Hz, 1 H, $NHOCH_2C_{6H5}$), 4.11 (dd, $J_{4,5}$ = 3.7 Hz, $J_{4,3}$ = 5.4 Hz, 1 H, H4), 4.03 (dd, $J_{3,2}$ = 7.1 Hz, $J_{4,3}$ = 5.4 Hz, 1 H, H3), 3.53 (m, 1 H, H5), 2.07, 2.02 (s, s, $OCOCH_3$), 2.01–1.90 (m, 2 H, H6, $J_{5,6(ax)} = J_{5,6(eq)}$ = 4.6 Hz), 1.52, 1.31 (s, s, $OC(CH_3)_2O$); MS m/z 378 (M^+ – 15, 2). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.92; N, 3.56. Found: C, 61.20; H, 6.74; N, 3.81. Compound 41 (393 mg, 1 mmol) was treated with excess sodium methoxide in methanol at room temperature for 24 h. The solvent was evaporated and the residue was dissolved in methylene chloride, washed with brine, dried, and evaporated. After flash chromatography of the residue (CH_2Cl_2/methanol, 95:5) we obtained compound 42 (275 mg, 70%): mp 95–97 °C; $[\alpha]^{25}_D$ +20° (c 1.3, $CHCl_3$); IR (KBr) 3490, 3470, 3300–3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, aromatic), 4.67 (s, 2 H, $NHOCH_2C_6H_5$), 4.14 (dd, $J_{4,5}$ = 3.9 Hz, $J_{3,4}$ = 5.9 Hz, 1 H, H4), 3.95 (dd, $J_{3,2}$ = 7.4 Hz, $J_{4,3}$ = 5.9 Hz 1 H, H3), 3.70 (td, $J_{1,2}$ = 8.9 Hz, $J_{1,6(eq)}$ = 6.0 Hz, $J_{1,6(ax)}$ = 8.9 Hz, 1 H, H1), 3.55 (dd, $J_{1,2}$ = 8.9 Hz, $J_{2,3}$ = 7.4 Hz, 1 H, H2), 3.47 (m, 1 H, H5), 3.40 (br s, 1 H), 1.87–1.79 (m, 2 H, H6); ^{13}C NMR (20 MHz, $CDCl_3$) δ 137.37, 128.67, 128.43, 128.05 (aromatic), 109.14 (C8), 79.15, 77.00, 75.01, 68.56, 56.73 (C1, C2, C3, C4, C5), 77.00 (C7), 31.26 (C6), 28.03, 25.78 (C9, C10); MS m/z 294 (M^+ – 15, 1). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.39; H, 7.44; N, 4.60.

Cyclization of Compound 12. Compound 12 (704 mg, 1.6 mmol) gave, after reaction (the hydride was added in 7 h) and chromatography (hexane/EtOAc, 4:1), 43 + 43[Cl(R)] (85 mg) and 43 (421 mg, 75%) as an oil: $[\alpha]^{25}_D$ –39° (c 2.1, $CHCl_3$); IR (film) 3500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H, aromatic), 5.86 (br, s, 1 H, $NHOCH_2C_6H_5$), 4.71 (s, 2 H, $NHOCH_2C_6H_5$), 4.40 (td, $J_{1,2} = J_{1,6(ax)}$ = 5.3 Hz, $J_{1,6(eq)}$ = 3.3 Hz, 1 H, H2), 3.61 (m, 1 H, H3), 3.40–3.30 (m, 2 H, H4, H5), 2.40 (ddd, $J_{6(eq),6(ax)}$ = 14.6 Hz, $J_{6(eq),5}$ = 4.8 Hz, $J_{6(eq),1}$ = 3.3 Hz, 1 H, H6(eq)), 1.82 (ddd, $J_{6(ax),1}$ = 5.3 Hz, $J_{6(ax),5}$ = 9.0 Hz, 1 H, H6(ax)), 1.49, 1.42, 1.41, 1.34 (s, s, s, s, 12 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 138.00, 128.34, 127.75 (aromatic), 111.26, 109.16 (C7, C8), 80.49, 78.61, 75.42, 74.33 (C1, C2, C3, C4), 76.99 ($NHOCH_2C_6H_5$), 57.86 (C5), 30.54 (C6), 28.20, 26.87, 25.69 (C9, C10, C11, C12); MS m/z 349 (M^+, 2). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.43; H, 7.68; N, 4.07. Compound 43 (500 mg, 1.4 mmol) was stirred with acetic acid/water (7:3, 10 mL) at room temperature 24 h. The solvent was evaporated and the residue submitted to chromatography (CH_2Cl_2/methanol, 90:10), giving compound 44 (279 mg, 70%): mp 137–139 °C; $[\alpha]^{25}_D$ –60° (c 0.3, $CHCl_3$); IR (KBr) 3600–3100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, aromatic), 4.67 (s, 2 H, $NHOCH_2C_6H_5$), 3.99 (q, J = 3.0 Hz, 1 H, H1), 3.56 (t, J = 9.3 Hz, 1 H, H3), 3.40–3.26 (m, 2 H, H2, H4), 3.07 (ddd, $J_{5,6(eq)}$ = 3.9 Hz, 1 H, H6(eq)), 1.61 (ddd, $J_{6(ax),6(eq)}$ = 13.9 Hz, $J_{6(ax),1}$ = 2.4 Hz, $J_{5,6(ax)}$ = 11.7 Hz, 1 H, H6(ax)); MS m/z 269 (M^+, 2). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.78; H, 7.04; N, 5.01. Compound 44 (19.5 mg, 0.72 mmol) dissolved in methanol (6 mL) was hydrogenated over 10% Pd/C at room temperature and 1 atm during 12 h. The catalyst was removed and washed with methanol, the solvent was evaporated, and the residue was acetylated (Ac_2O/pyridine, 24 h, rt). After evaporation and chromatography (hexane/EtOAc, 4:1) we obtained compound 46 (161 mg, 59%): mp 37–39 °C; $[\alpha]^{25}_D$ –9.6° (c 6.5, $CHCl_3$); IR (KBr) 3360, 1750, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 8.8 Hz, 1 H, NHAc), 5.47 (t, $J_{2,3} = J_{3,4}$ = 10.1 Hz, 1 H, H3), 5.38 (q, $J_{1,6(ax)} = J_{1,6(eq)} - J_{1,2}$ = 3.0 Hz, 1 H, H1), 4.90 (t, $J_{3,4} = J_{4,5}$ = 10.1 Hz, 1 H, H4), 4.87 (dd, $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 10.1 Hz, 1 H, H2), 4.42 (m, 1 H, H5), 2.20 (td, $J_{6(eq),6(ax)}$ = 14.7 Hz, $J_{6(eq),1} = J_{6(eq),5}$ = 3.1 Hz, 1 H, H6(eq)), 2.12, 2.02, 1.99, 1.95, 1.89 (s, s, s, s, s, 15 H), 1.56 (ddd, $J_{6(eq),6(ax)}$ = 14.7 Hz, $J_{6(ax),1}$ = 2.2 Hz, $J_{6(ax),5}$ = 12.5 Hz, 1 H, H6(ax)); MS m/z 373 (M^+, 2). Anal. Calcd for $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75. Found: C, 51.27; H, 6.29; N, 3.46.

Free Radical Cyclization of 14. Compound 14 (370 mg, 1.0 mmol) was submitted to the usual standard procedure for cyclization. The hydride was added in 6 h. Flash chromatography (hexane/EtOAc, 95:5) gave 47 + 47[Cl(R)] (20 mg) and 47 (165 mg, 60%) as an oil: $[\alpha]^{25}_D$ –58° (c 1.8, $CHCl_3$); IR (film) 2990, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (td, $J_{5,6(eq)}$ = 2.4 Hz, $J_{5,6(ax)} = J_{5,4}$ = 5.2 Hz, 1 H, H5), 4.14 (dd, $J_{5,4}$ = 5.2 Hz, $J_{4,3}$ = 8.5 Hz, 1 H, H4), 3.56 (dd, $J_{4,3}$ = 8.5 Hz, $J_{3,2}$ = 9.7 Hz, 1 H, H3), 3.45 (m, 2 H, CH_2OCH_3), 3.35 (s, CH_2OCH_3), 3.21 (t, $J_{2,3} = J_{2,1}$ = 9.7 Hz, H1, H2), 2.27 (ddd, $J_{6(eq),6(ax)}$ = 15.4 Hz, $J_{6(eq),5}$ = 2.4 Hz, $J_{6(eq),1(ax)}$ = 5.1 Hz, 1 H, H6(eq)), 2.12 (m, 1 H, H1), 1.72 (ddd, $J_{6(ax),1}$ = 10.6 Hz, $J_{6(ax),5}$ = 5.2 Hz, 1 H, H6(ax)), 1.50, 1.42, 1.41, 1.35 (s, s, s, s, 12 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.47, 108.93 (C7, C8), 81.63, 77.62, 76.06, 74.43 (C2, C3, C4, C5), 73.03 (C13), 58.99 (C14), 36.61 (C1), 29.12 (C6), 28.38, 26.92, 25.96 (C9, C10, C11, C12); MS m/z 272 (M^+, 5). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.57; H, 8.59. Compound 47 (358 mg, 1.3 mmol) was treated with acetic acid/water (7:3, 8 mL) at room temperature for 24 h. The solvent was evaporated and the residue submitted to chromatography (CH_2Cl_2/methanol, 90:10), giving compound 50 (173 mg, 70%): mp 98–100 °C; $[\alpha]^{25}_D$ –57° (c 0.5, CH_3OH); IR ($CHCl_3$) 3500–3200, 1070 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.94 (dd, J = 3.2 and 2.4 Hz, 1 H, H5), 3.54 (t, J = 9.4 Hz, 1 H, H3), 3.46 (m, 2 H, CH_2OCH_3), 3.30 (s, 3 H, CH_2OCH_3), 3.25 (dd, J = 3.2 and 9.4 Hz, 1 H, H4), 3.18 (dd, J = 9.4 and 10.5 Hz, 1 H, H2), 1.98 (m, 1 H, H1), 1.84 (td, J = 3.2 and 14.4 Hz, 1 H, H6(eq)), 1.38 (ddd, J = 14.4, 13.0, and 2.4 Hz). Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 49.71; H, 8.16.

Free Radical Cyclization of 15. Compound 15 (244 mg, 0.64 mmol) was submitted to the usual conditions. The hydride was added in 3 h. After flash chromatography (hexane:EtOAc, 90:10) we obtained 48 + 48[Cl(R)] (15 mg) and 48 (134 mg, 80%) and 49 (15 mg, 7%). 48: mp 75–77 °C; $[\alpha]^{25}_D$ –61° (c 1.2, $CHCl_3$); IR (KBr) 2875, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (td, $J_{5,4} = J_{5,6(ax)}$ = 5.2 Hz, $J_{5,6(eq)}$ = 1.5 Hz, 1 H, H5), 4.14 (dd, $J_{4,3}$

= 8.6 Hz, $J_{4,5}$ = 5.2 Hz, 1 H, H4), 3.68 (s, 3 H, COOCH_3), 3.56 (dd, $J_{4,3}$ = 8.6 Hz, $J_{3,2}$ = 9.7 Hz, 1 H, H3), 3.06 (t, $J_{2,3}$ = $J_{2,1}$ = 9.7 Hz, 1 H, H2), 2.70 (dd, $J_{13,13'}$ = 15.0 Hz, $J_{13,1}$ = 3.8 Hz, 1 H, H13), 2.50-2.28 (m, 2 H, H1, H6(eq)), 2.20 (dd, $J_{13,13'}$ = 15.0 Hz, $J_{13',1}$ = 8.8 Hz, 1 H, H13'), 1.51, 1.40, 1.39, 1.35 (s, s, s, s, 12 H), 1.50-1.45 (m, 1 H, H6(ax)); ^{13}C NMR (20 MHz, $CDCl_3$) δ 171.99 ($COOCH_3$), 110.35, 108.92 (C7, C8), 81.69, 78.56, 77.60, 74.20 (C2, C3, C4, C5), 51.40 ($COOCH_3$), 36.94 (C6), 33.16 (C1), 31.59 (C13), 28.38, 26.78, 25.97 (C9, C10, C11, C12); MS m/z 285 (M^+ - 15, 18). Anal. Calcd for $C_{15}H_{24}O_6$: C, 58.31; H, 8.39. Found: C, 58.22; H, 8.31. **49**: mp 35-37 °C; $[\alpha]^{25}_D$ -10° (c 0.6, $CHCl_3$); IR ($CHCl_3$) 2990, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, $J_{2,3}$ = 4.0 Hz, $J_{2,1}$ = 15.8 Hz, 1 H, H2), 6.15 (dd, $J_{1,2}$ = 15.8 Hz, $J_{1,3}$ = 2.0 Hz, 1 H, H1), 4.66 (ddd, $J_{3,2}$ = 4.0 Hz, $J_{3,1}$ = 2.0 Hz, $J_{3,4}$ = 2.4 Hz, 1 H, H3), 3.78 (dd, $J_{5,4}$ = 2.4 Hz, $J_{6,5}$ = 5.4 Hz, 1 H, H5), 3.74 (s, 3 H, COOCH_3), 3.72 (m, 1 H, H6), 3.60 (t, $J_{3,4}$ = $J_{4,5}$ = 2.4 Hz, 1 H, H4), 1.47, 1.45, 1.41, 1.31 (s, s, s, s, 12 H), 1.28 (d, J = 5.9 Hz, 3 H, CH_3-7); MS m/z 285 (M^+ -15, 13). Anal. Calcd for $C_{15}H_{24}O_6$: C, 58.21; H, 8.39. Found: C, 57.99; H, 8.26. Compound **48** (252 mg, 0.8 mmol) was treated with acetic acid/water (7:3, 7 mL) and stirred at room temperature for 24 h. The solvent was evaporated and the residue submitted to chromatography (CH_2Cl_2/methanol, 90:10), giving the polyol **51** (118 mg, 68%): mp 113-115 °C; $[\alpha]^{25}_D$ -52° (c 0.4, CH_3OH); IR (KBr) 3600-3200, 2975, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (ddd, $J_{5,6(eq)}$ = 3.6 Hz, $J_{5,6(ax)}$ = 2.2 Hz, $J_{5,4}$ = 3.2 Hz, 1 H, H5), 3.83 (s, 3 H, COOCH_3), 3.74 (t, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, 1 H, H3), 3.48 (dd, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 3.2 Hz, 1 H, H4), 3.21 (dd, $J_{2,3}$ = 9.2 Hz, $J_{2,1}$ = 10.4 Hz, 1 H, H2), 2.91 (dd, $J_{7,7'}$ = 14.6 Hz, $J_{7,1}$ = 4.0 Hz, 1 H, H7), 2.44 (m, 1 H, H1), 2.32 (dd, $J_{7,7'}$ = 14.6 Hz, $J_{7',1}$ = 8.7 Hz, 1 H, H7'), 2.05 (td, $J_{6(eq),6(ax)}$ = 14.2 Hz, $J_{6(eq),1}$ = $J_{6(eq),5}$ = 3.6 Hz, 1 H, H6(eq)), 1.47 (ddd, $J_{6(ax),5}$ = 2.2 Hz, $J_{6(ax),6(eq)}$ = 14.2 Hz, $J_{6(ax),1}$ = 11.5 Hz, 1 H, H6(ax)). Anal. Calcd for $C_9H_{16}O_6$: C, 49.08; H, 7.32. Found: C, 48.91; H, 7.01.

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Supplementary Material Available: Synthetic procedures and spectral data of the intermediates in the preparation of compounds 4-16 (19 pages). This material is contained in many 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.

Metal-Ammonia Reduction and Reductive Alkylation of *N*-Alkylnaphthalenesulfonamides. A New Route to Substituted Naphthalenes[1]

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Conditions have been found for 1,4-reduction of aromatic sulfonamides (conveniently monitored by electrical conductivity), using metals in THF/liquid ammonia on the pre-formed *N*-lithium salts (BuLi), without concomitant C-S reductive cleavage. The resulting 1,4-dihydro compounds could be alkylated, either in situ (in the case of simple unfunctionalized halides only) or, following isolation, after further N-alkylation and then forming the monoanion, or after forming the dianion of the N-monoalkylated dihydrosulfonamide, generally using as base *n*-butyllithium (a simple titration procedure). In the former case functionalized electrophiles (bromo esters, chloroformates) could be utilized. The ratio of α- to γ-alkylation was dependent on the method of alkylation, the reaction medium, the nature of the N-alkyl group(s), and whether a monoanion or a dianion served as substrate. γ-Alkylation products could in some cases be further α-substituted. The α-substituted products aromatized, with loss of SO_2 and amine, by heating, whereas γ-substitution products required hydrolysis by aqueous alkali; this greatly facilitated separation where mixtures were formed. Thus, this dihydrosulfonamide route constitutes a novel and nucleophilic route to 1-substituted, 2-substituted, and, notably, 1,3-disubstituted naphthalenes.

Introduction

The Birch reduction by metals in liquid ammonia continues to be the most effective way of transforming an aromatic system into alicyclic and, ultimately, acyclic compounds.[2] It proceeds with particular ease (with little or no proton donor required) when the aromatic ring is substituted by electron-withdrawing groups, such as carboxyl,[3] carboxylic ester,[4] carboxamide,[5] nitrile,[6] and, noticeably, ketone.[7] In most cases the experimental conditions permit the trapping of a stable carbanion intermediate by an electrophile such as alkyl or alkenyl halide,[2b] epoxide,[8] or α,β-unsaturated ester even when a limited amount of proton donor may have to be present to avoid side reactions.[4-7] This adds greatly to the usefulness of the reaction, particularly when followed by further, often

(1) For a preliminary communication, see: Gottlieb, L.; Loewenthal, H. J. E. *Tetrahedron Lett.* **1988**, *29*, 4473.

(2) For recent reviews on the synthetic utility of the Birch reduction see: (a) Dryden, H. L. Reduction of Steroids by Metal-Ammonia Solutions. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. 1, p 1. (b) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, 35.

(3) (a) Bachi, M. D.; Epstein, J. W.; Loewenthal, H. J. E. *Tetrahedron Lett.* **1966**, 5333. (b) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34*, 126.

(4) (a) Loewenthal, H. J. E. *Guide for the Perplexed Organic Experimentalist*; Heyden: London, 1978; p 136. (b) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1097.

(5) (a) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.* **1984**, *49*, 4429. (b) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915.

(6) Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983.

(7) Narisada, M.; Watanabe, F. *J. Org. Chem.* **1973**, *38*, 3887.

(8) Sipio, W. J. *Tetrahedron Lett.* **1985**, *26*, 2039.

(9) Rao, G. S. R. S.; Ramanathan, H.; Raj, K. *J. Chem. Soc., Chem. Commun.* **1980**, 315.

0022-3263/92/1957-2631$03.00/0