COMMUNICATION

Dispiroketals in synthesis. Part 23.[1] A new route to (+)-D-conduritol B from *myo*-inositol

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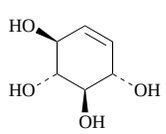
Using (2*S*,2′*S*)-2,2′-diphenyl-6,6′-bi(3,4-dihydro-2*H*-pyran) to effect a simultaneous protection–resolution of a *myo*-inositol derivative, a new synthesis of (+)-D-conduritol B has been achieved.

Conduritols and their derivatives have attracted considerable attention from synthetic chemists owing to their diverse biological activity.[2–6] Conduritol B is the least accessible of the chiral conduritols because it is the only one which does not possess a *cis*-vicinal diol pair, thus making it less amenable to the two most common synthetic strategies, the action of *Pseudomonas putida* on aromatic precursors[7] and the asymmetric dihydroxylation reaction of Sharpless.[8] Five different asymmetric approaches to conduritol B have been reported.[9] We describe here a new route to (+)-D-conduritol B **1** using



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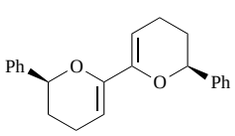

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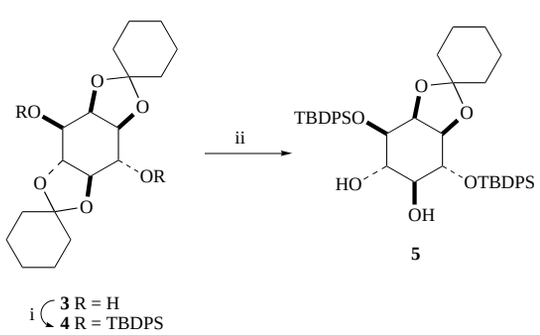
(2*S*,2′*S*)-2,2′-diphenyl-6,6′-bi(3,4-dihydro-2*H*-pyran) **2**[10] to effect the simultaneous resolution and protection of a *myo*-inositol-derived diol, a strategy which has the potential to offer equal access to both enantiomers.

We have demonstrated previously the use of dispiroketals in synthesis, especially in the carbohydrate area and in the generation of enantiomerically-enriched compounds from racemic or *meso* diols.[10] Useful results continue to be produced as new generations of substituted bi(dihydropyran)s are developed and become commercially available.† Furthermore, related chemistry using other 1,2-diacetals, which we introduced some years ago, is beginning to impact upon the area.[11]

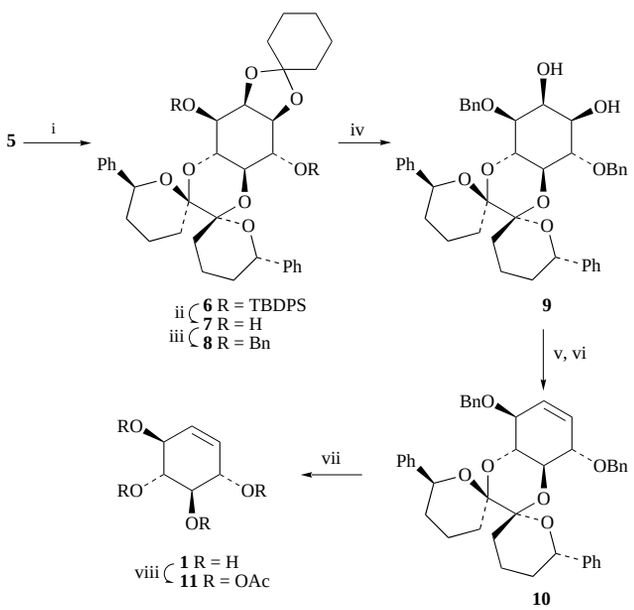
Racemic 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol **3**, which is available in one step from *myo*-inositol,[12] is the starting point for the current synthesis. Protection of **3** with *tert*-butyldiphenylsilyl (TBDPS) groups to give **4** followed by cleavage of the *trans*-cyclohexylidene acetal results in diol **5** (Scheme 1).



Scheme 1 *Reagents and conditions:* i, TBDPSCl (10 equiv.), pyridine (excess), reflux, 16 h, 72%; ii, ethylene glycol (1 equiv.), toluene-*p*-sulfonic acid (cat.), $CHCl_3$, 50 °C, 1.5 h, 76%

† Unsubstituted diene 6,6′-bi(3,4-dihydro-2*H*-pyran) is available from the Aldrich Chemical Company.

TBDPS protection was chosen to enhance the solubility of the resulting diol in chloroform, the solvent used for the subsequent dispiroketalisation. Derivatives with different protection had given poor results due to the insolubility of the substrate; diol **5**, however, was completely soluble in chloroform and reacted with (2*S*,2′*S*)-2,2′-diphenyl-6,6′-bi(3,4-dihydro-2*H*-pyran) **2** to give the corresponding dispiroketal **6** (Scheme 2).



Scheme 2 *Reagents and conditions:* i, **2** (0.51 equiv.), PPh_3·HBr (cat.), $CHCl_3$, room temp., 96 h, 35% (70% based on theoretical maximum for a resolution); ii, Bu_4NF (2 equiv.), THF, 60 °C, 10 h, quant.; iii, NaH (2.5 equiv.), DMF, 0 °C, 1 h, then Bu_4NI (cat.), BnBr (2.4 equiv.), room temp., 36 h, 61%; iv, 1-sulfanylpropan-2-ol (3 equiv.), BF_3·OEt_2 (1 equiv.), $CHCl_3$, 45 °C, 40 min, quant. (ref. 14); v, thiocarbonyldiimidazole (2 equiv.), DMAP (cat.), PhMe, reflux, 16 h, 97%; vi, $P(OMe)_3$, reflux, 5 h, quant.; vii, Li (*ca.* 10 equiv.), NH_3(1), Et_2O, −78 °C, 2 h, quant.; vii, Ac_2O, pyridine, room temp. 16 h, quant.

This reaction constitutes a simultaneous resolution and protection of the racemic diol **5**. The complete diastereoselectivity of the reaction (the product **6** is a single diastereoisomer by ^1H and ^{13}C NMR spectroscopy) is a consequence of a chirality match, only one diastereoisomer of **6** allowing an all-chair structure with all substituents equatorial and full anomeric stabilisation at the newly-formed spiro centres (Fig. 1).[10]

The resolution–protection proceeds in a good 70% yield (based on the theoretical maximum for a resolution). The other enantiomer of diol **5** does not react with **2** because its chirality is mis-matched; it is readily removed by chromatography, an advantage over conventional resolutions which frequently involve a tedious separation of diastereoisomers. As the bulky TBDPS groups prevented further transformations later in the synthesis they were removed to afford diol **7**, which was dibenzylated to provide the less sterically encumbered derivative **8**. It should be noted that it was not possible to have the benzyl

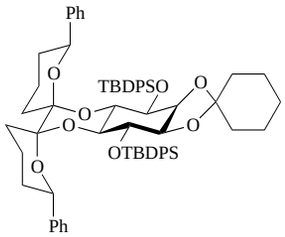


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Fig. 1

protecting groups in place from the beginning since they did not have sufficient solubilising effect to allow the dispiroketalisation to proceed. Cleavage of the remaining cyclohexylidene group[13] in **8** gave diol **9** which was converted, according to the Corey–Winter procedure,[14] to alkene **10**. Finally, treatment with lithium in liquid ammonia achieved global deprotection to afford the target molecule **1** in quantitative yield (purification on reversed phase silica gel). Conversion of **1** to tetra-*O*-acetylconduritol B **11** gave a less polar material which was easier to handle. While the melting points and the proton and carbon NMR spectra of **11** were in accordance with the literature,[9a,b] the optical rotation {$[\alpha]_D^{25}$ +70.0 (*c* 0.85, $CHCl_3$)} was far too low compared to literature values {for the (−)-isomer, $[\alpha]_D^{20}$ −176.8 (*c* 1.18, $CHCl_3$)[9a] and $[\alpha]_D^{20}$ −172.4 (*c* 1.2, $CHCl_3$)[9b]}. A second purification by sublimation did not alter the value of the rotation. For this reason a sample of racemic conduritol B‡ was peracetylated and chiral GC was found to give clear separation of the enantiomers. When our synthetic material was compared with the racemic material using this technique only one enantiomer was detectable. A double-injection experiment proved that our synthetic material consisted of a single enantiomer of conduritol B.

We estimate the enantiomeric excess to be >99% by this method. The discrepancy between our value for the optical rotation and the literature is attributed either to a strongly rotating impurity present in very small amount, to concentration effects or to incorrect determination of the literature values. No chiral GC studies were described in these cases.[9a,b]

Experimental

Preparation of 1-L-(2′*S*,2″*S*,6′*S*,6″*S*)-1,4-di-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-cyclohexylidene-5,6-*O*-[6′,6″-diphenyl-3′,3″,4′,4″,5′,5″,6′,6″-octahydro-2′,2″-bi(2*H*-pyran-2′,2″-diyl)]-*myo*-inositol 6

Diol **5** (1.14 g, 1.54 mmol) and diene **2** (225 mg, 0.708 mmol, 0.51 eq.) were dried by azeotroping with anhydrous toluene. The crystalline residue was dissolved in chloroform (freshly distilled from calcium hydride), triphenylphosphonium bromide (a few crystals, catalytic) was introduced and the solution was stirred at room temp. over 72 h, with addition of a further portion of triphenylphosphonium bromide after each 24 h period. Silica gel (*ca.* 10 g) was then added, the solvent was removed *in vacuo* and the resulting powder was dry-loaded onto a packed silica gel column. Flash column chromatography with gradient elution (compounds listed in order of elution with their eluent) gave (with 2% Et_2O–light petroleum) the *dispiroketalised* myo-*inositol* **6** (570 mg, 70% based on theoretical maximum 50% yield of one diastereoisomer) as a white foam; $[\alpha]_D^{24}$ −13.2 (*c* 1.03, $CHCl_3$) (Found: C, 75.03; H, 7.44. $C_{66}H_{78}O_8Si_2$ requires C, 75.10; H, 7.45%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3153, 3028, 2933, 2856, 1463, 1379, 1162, 1135, 1104, 1064; δ_H(500 MHz; $CDCl_3$) [1.07 (9 H, s) and 1.08 (9 H, s), 2 × Bu^t], [1.12–1.41 (14 H, m), 1.43–1.57 (2 H, m), 1.61–1.72 (2 H, m), 1.74–1.83 (2 H, m) and 1.89–2.05 (2 H, m), 11 × CH_2], 3.35 (1 H, t, *J* 9.9, 5-H), 3.56 (1 H, t, *J* 4.1, 2-H), 3.66–3.73 (2 H, m, two out of 1-H or 3-H and 4-H or 6-H), 3.89 (1 H, t, *J* 9.9, one of 4-H or 6-H), 3.98 (1 H, dd, *J* 9.9, 4.1, one of 1-H or 3-H), [4.71–4.76 (1 H, m) and 4.86–4.92 (1 H, m), 2 × dispoke CHPh], [7.15–7.45 (22 H, m), 7.57–7.60 (2 H, m), 7.73–7.77 (2 H, m) and 7.82–7.89 (4 H, m), 30 × dispoke and silyl Ar-H]; δ_C(100 MHz; $CDCl_3$; asterisk indicates overlapping signals as judged by relative intensities) 17.4 and 18.7 [2 × Si*C*$(CH_3)_3$], 19.3, 19.7, 23.7, 23.9 and 25.1 (5 × CH_2), 26.9 and 27.2 [2 × SiC$(CH_3)_3$], 27.8, 28.1, 31.6, 33.4, 35.1 and 37.3 (6 × CH_2), 67.5, 68.9, 70.1, 70.2, 70.5, 75.4, 75.9 and 79.5 (1-C, 2-C, 3-C, 4-C, 5-C, 6-C and 2 × dispoke CHPh), 96.9* (dispoke acetal C), 109.4 (cyclohexylidene acetal C), 125.5, 126.0, 126.8, 126.9, 127.0, 127.1, 127.3, 127.5, 128.1*, 128.2, 128.9, 129.4 and 129.7 (dispoke *ortho*-, *meta*- and *para*-C and silyl *meta*- and *para*-C), 131.9*, 133.8 and 134.2 (silyl *ipso*-C), 135.8, 136.2* and 137.3 (silyl *ortho*-C), 143.4 and 144.1 (dispoke *ipso*-C); *m*/*z* (+FAB) 1078 (M + Na)$^+$, 840 (M + Na − TBDPS)$^+$, 661, 603, 563, 485, 407, 319, 253 [HRMS (+FAB) on (M + Na)$^+$: found, 1077.5167. $C_{66}H_{78}O_8Si_2Na$ requires 1077.5133]; and (with 20% EtO–light petroleum) unreacted starting material (376 mg, 33%), spectroscopically identical to that isolated previously.[15]

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References

1 Part 22: S. V. Ley, S. Mio and B. Meseguer, *Synlett*, 1996, 791.
2 D. C. Billington, F. Perron-Sierra, I. Picard, S. Beaubras, J. Duhalt, J. Espinal and S. Challal, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2307.
3 G. Legler, *Methods Enzymol.*, 1977, **46**, 368.
4 G. Legler and M. Herrchen, *FEBS Lett.*, 1981, **135**, 139.
5 G. Legler and R. Bollhagen, *Carbohydr. Res.*, 1992, **233**, 113.
6 Z.-X. Guo, A. H. Haines, S. M. Pyke, S. G. Pyke and R. J. K. Taylor, *Carbohydr. Res.*, 1994, **264**, 147.
7 See, for example; (*a*) S. V. Ley, M. Parra, A. J. Redgrave and F. Sternfeld, *Tetrahedron*, 1990, **46**, 4995; (*b*) T. Hudlicky, H. Luna, H. F. Olivio, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2907.
8 See, for example, R. Angelaud and Y. Landais, *J. Org. Chem.*, 1996, **61**, 5020.
9 (*a*) H. Paulsen, W. Röben and F. R. Heiker, *Chem. Ber.*, 1981, **114**, 3342; (*b*) C. Le Drain, J.-P. Vionnet and P. Vogel, *Helv. Chim. Acta*, 1990, **73**, 161; (*c*) T. Akiyama, H. Shima and S. Ozaki, *Tetrahedron Lett.*, 1991, **32**, 5593; (*d*) L. Yu, R. Cabrera, J. Ramirez, V. A. Malinovskii, K. Brew and P. G. Wang, *Tetrahedron Lett.*, 1995, **36**, 2897; (*e*) Two almost identical approaches; N. Chida, M. Ohtsuka, K. Nakazawa and S. Owaga, *J. Chem. Soc., Chem. Commun.*, 1989, 436; K.-I. Sato, M. Bokura and M. Taniguchi, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1633.
10 For a review of the synthesis and chemistry of dispiroketals, see S. V. Ley, R. Downham, P. J. Edwards, J. E. Innes and M. Woods, *Contemp. Org. Synth.*, 1995, 365.
11 N. L. Douglas, S. V. Ley, H. M. I. Osborn, D. R. Owen, H. W. M. Priepke and S. L. Warriner, *Synlett*, 1996, 793 and references cited therein.
12 C. Jiang and D. C. Baker, *J. Carbohydr. Chem.*, 1986, **5**, 615.
13 K. S. Bruzik and M.-D. Tsai, *J. Am. Chem. Soc.*, 1992, **114**, 6361.
14 E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, 1963, **85**, 2677.
15 J. E. Innes, Ph.D. Thesis, University of Cambridge, 1996.

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