Pergamon

Tetrahedron Letters 42 (2001) 8081–8083

TETRAHEDRON LETTERS

Chiral base route to cyclic polyols: asymmetric synthesis of aminodeoxyconduritols and conduritol F

Simon E. de Sousa, Peter O'Brien* and Christopher D. Pilgram

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

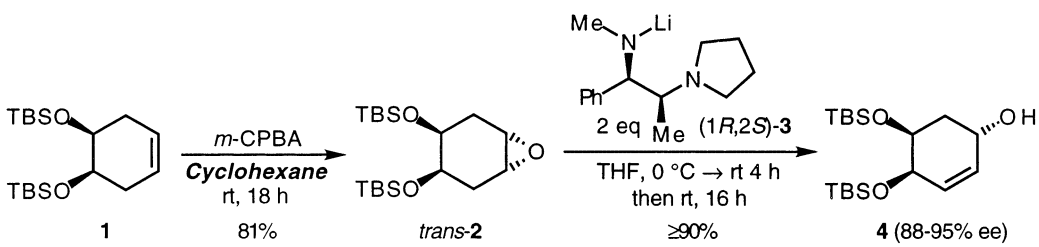
Received 9 August 2001; accepted 7 September 2001

Abstract—A chiral base route from a *meso* cyclohexene oxide to an allylic alcohol provides key intermediates for the synthesis of cyclic polyols. A Mitsunobu approach and an Overman rearrangement approach transform allylic alcohols into some aminodeoxyconduritols (95% ee). Elaboration of a chiral enone (89% ee) via (i) α-hydroxylation and (ii) stereoselective reduction completes a high yielding synthesis of the tetraacetate of conduritol F.

The asymmetric synthesis of conduritols and related cyclitols continues to attract considerable interest[1–3] as these compounds possess a range of useful biological activity (e.g. insulin modulators and glycosidase inhibitors).[4] There has also been recent interest in the preparation of amino conduritols.[5] For the last few years, we have been developing a concise, simple and stereocontrolled entry into highly functionalised polyhydroxylated cyclohexenes.[6–8] Our approach involves epoxidation of cyclohexene **1** to give epoxide *trans*-**2** followed by a chiral base-mediated desymmetrisation reaction to generate allylic alcohol **4** in high enantiomeric excess. We were particularly keen to extend our methodology to the synthesis of some aminoconduritol analogues and the tetraacetate of naturally occurring (+)-conduritol F. These topics, together with some new features of our route, are reported in this paper (Scheme 1).

Although we have previously reported in detail the stereoselective epoxidation of cyclohexenes like **1**,[9] we had not described an efficient large scale synthesis of epoxide *trans*-**2**. Recently, we found that *m*-CPBA epoxidation of **1** in *cyclohexane* proceeded with high *trans* stereoselectivity (93:7 mixture of *trans*- and *cis*-**2**)[10] and this allowed us to isolate consistently high yields of epoxide *trans*-**2** (81%) on a multi-gram scale. Enantioselective rearrangement of epoxide *trans*-**2** using chiral base (1*R*,2*S*)-**3**, independently developed by Ahlberg et al.[11] and ourselves,[6] gave reproducible multi-gram quantities of allylic alcohol **4** in ≥90% yield and 88–95% ee. In order to achieve ≥94% ee of allylic alcohol **4** for larger scale reactions (10 mmol of *trans*-**2**), it was important to add the epoxide slowly to the chiral base solution and to keep the temperature between 0 and −10°C during the addition. The diamine corresponding to chiral base (1*R*,2*S*)-**3** could easily be recovered (≥70%) by simple acid–base extraction.

Another limitation of our previously reported methodology was the inability to access epoxide *cis*-**2** in a stereoselective and high yielding fashion. To address this, we decided to investigate an oxidation–reduction sequence with allylic alcohol **4** as outlined below.

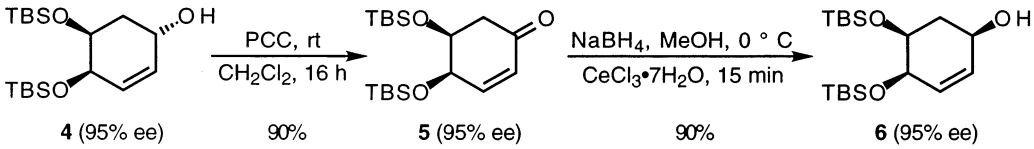


Scheme 1.

Keywords: allylic alcohols; cyclitols; epoxides; rearrangement.

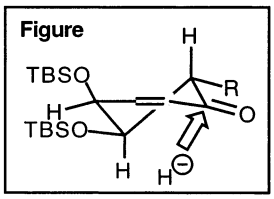
* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01706-3

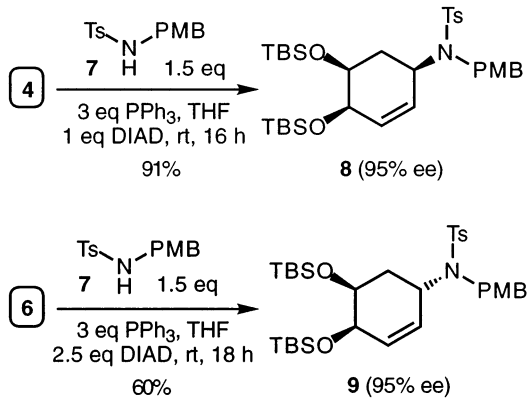


Scheme 2.

Allylic alcohol **4** (95% ee) was oxidised using PCC to give enone **5** in 90% yield. Subsequent reduction under Luche conditions furnished a 90% yield of allylic alcohol **6** as a single diastereoisomer. As is shown in the figure (R = H), the stereoselectivity is rationalised by axial attack on a preferred conformation of enone **5**. Thus, using our new epoxidation conditions and this redox sequence, we have developed efficient enantio- and diastereocontrolled routes to allylic alcohols **4** and **6** (Scheme 2).

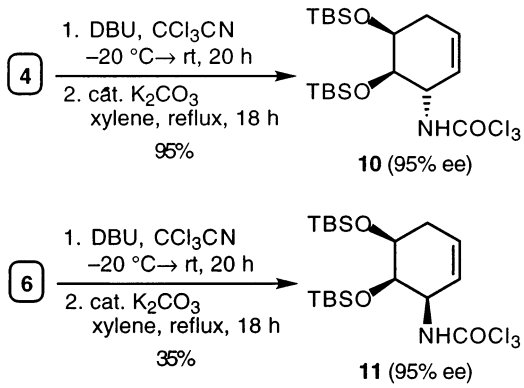


Two different methods were explored for the conversion of allylic alcohols **4** and **6** into amino conduritol analogues. The first approach involved standard Mitsunobu substitution with an appropriate nitrogen-derived nucleophile. A screen of the known[12] reagents indicated that the Fukuyama-like TsNHPMB **7** was the reagent of choice. Under standard Mitsunobu conditions using DIAD (optimised for each substrate), allylic alcohols **4** and **6** gave allylic sulfonamides **8** (91% yield) and **9** (60% yield), respectively. The absence of the other diastereoisomer in each of these reactions indicated the expected stereospecificity of the reactions (Scheme 3).



Scheme 3.

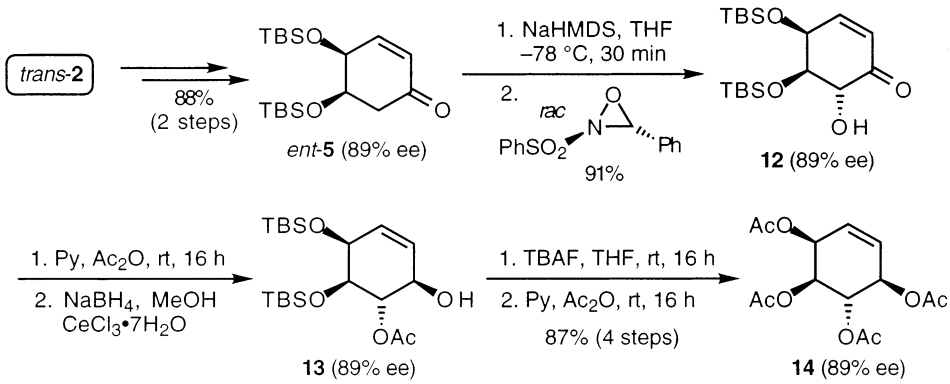
The second approach utilised Overman rearrangement reactions[13] and enabled regioisomeric allylic carbamates to be prepared. First of all, allylic alcohol **4** was converted into the required acetimidate upon treatment with trichloroacetonitrile and DBU. Then, without isolation, the crude acetimidate was heated in xylene with added potassium carbonate (Isobe's modification[14]) to give the rearranged allylic carbamate **10** in high yield. In contrast, the rearrangement of allylic alcohol **6** was less successful giving allylic carbamate **11** in only 35% yield. The reduced yield can be ascribed to the steric interactions encountered as the carbamate group rearranges towards the bulky silyoxy group in producing **11** (Scheme 4).



Scheme 4.

As a final demonstration of the utility of the chiral base chemistry in synthesis, we have completed a concise total synthesis of the tetraacetate of conduritol F.[1,2] In order to synthesise the naturally occurring enantiomer, enone *ent*-**5** was required. Enone *ent*-**5** (89% ee) was prepared in high yield by rearrangement of epoxide *trans*-**4** with chiral base (1*S*,2*R*)-**3** and subsequent PCC oxidation. α-Hydroxylation of enone *ent*-**5** was accomplished by deprotonation with sodium hexamethyldisilazide and enolate trapping with Davis' oxaziridine.[15] Interestingly, no β-elimination of the silyloxy group was observed and a high yield of a single diastereoisomer of hydroxy ketone **12** (91%) was obtained. The relative stereochemistry was determined by X-ray analysis of the acetate of **12** and presumably arises by enolate attack *trans* to the bulky silyloxy groups, one of which must occupy an axial position (Scheme 5).

Acetylation of hydroxy ketone **12** and then Luche reduction afforded alcohol **13** as the only product in quantitative yield. Axial attack of hydride on a preferred conformation of the enone (see figure, R = OAc) accounts for the stereoselectivity in a similar fashion to the reduction of enone **5** described previously. Finally, TBAF deprotection and a final acetylation yielded conduritol F tetraacetate **14** (89% ee) in an overall 87% yield over the last four steps of the synthesis. The synthetic material exhibited $[\alpha]_D$ +46.9 (*c* 1.0 in $CHCl_3$)



Scheme 5.

(lit.,[16] $[\alpha]_D$ +45.6 (*c* 1.1 in $CHCl_3$)) and was identical spectroscopically to the tetraacetate of the natural (+)-conduritol F thus corroborating our assignment of relative stereochemistry in **13** and **14**.

To summarise, crucial practical improvements to the synthesis of allylic alcohol **4** (95% ee) and its diastereoisomer **6** (95% ee) have been described. The usefulness of these compounds for the preparation of amino conduritol analogues and a high yielding synthesis of (+)-conduritol F has also been demonstrated. Our results suggest that enone **5** should now be regarded as a useful chiral building block for synthesis.

Acknowledgements

We thank the EPSRC for a grant (to S.E.dS.) and a project studentship (to C.D.P.; reference GR/L 58439).

References

1. Jørgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630–4634.
2. Cerè, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225–1231.
3. (a) Mehta, G.; Mohal, N.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3505–3508; (b) Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509–3512; (c) Kee, A.; O'Brien, P.; Pilgram, C. D.; Watson, S. T. *Chem. Commun.* **2000**, 1521–1522; (d) Honzumi, M.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1999**, 1985–1986; (e) Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *Chem. Commun.* **1998**, 1945–1946.
4. Hudlicky, T.; Cebulak, M. *Cyclitols and Derivatives*; VCH: New York, 1993.
5. (a) Trost, B. M.; Dudash, J.; Hembre, E. J. *Chem. Eur. J.* **2001**, *7*, 1619–1629; (b) Arcelli, A.; Cerè, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2001**, *57*, 3439–3444; (c) Desjardins, M.; Lallemand, M. C.; Freeman, S.; Hudlicky, T.; Abboud, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 628; (d) Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Am. Chem. Soc.* **1998**, *120*, 1732–1740.
6. de Sousa, S. E.; O'Brien, P.; Stefens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423–8425.
7. Colman, B.; de Sousa, S. E.; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175–4182.
8. de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483–1492.
9. (a) de Sousa, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett.* **1999**, *40*, 387–390; (b) de Sousa, S. E.; O'Brien, P.; Pilgram, C. D.; Roder, D.; Towers, T. D. *Tetrahedron Lett.* **1999**, *40*, 391–392.
10. For a related epoxidation in cyclohexane, see: Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402–1408.
11. Petterson, D.; Amedjkouh, M.; Nilsson Lill, S. O.; Dahlén, K.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1654.
12. (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656; (b) Bell, K. E.; Knight, D. W.; Gravestock, M. B. *Tetrahedron Lett.* **1995**, *36*, 8681–8684; (c) Decicco, C. P.; Grover, P. *Synlett* **1997**, 529–530; (d) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900–2903; (e) Berrée, F.; Michelot, G.; Le Corre, M. *Tetrahedron Lett.* **1998**, *39*, 8275–8276; (f) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709–5712; (g) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374; (h) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831–5834.
13. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910.
14. Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.
15. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241–3243.
16. Le Drian, C.; Vionnet, J.-P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161–168.