



Pergamon

Tetrahedron Letters 41 (2000) 4453–4456

TETRAHEDRON
LETTERS

A brief synthesis of the Aplasmomycin tetrahydrofuran

Sean P. Bew, David W. Knight* and Robert J. Middleton

Department of Chemistry, Cardiff University, PO Box 912, Cardiff, CF10 3TB, UK

Received 29 February 2000; accepted 10 April 2000

Abstract

A highly stereoselective iodocyclisation of the 3-alkene-1,2-diol **9**, derived from asymmetric dihydroxylation of the dienyl benzoate **8**, gives the β -iodotetrahydrofuran **10** and thence the Aplasmomycin precursor **13**, following deiodination and Mitsunobu inversion. © 2000 Elsevier Science Ltd. All rights reserved.

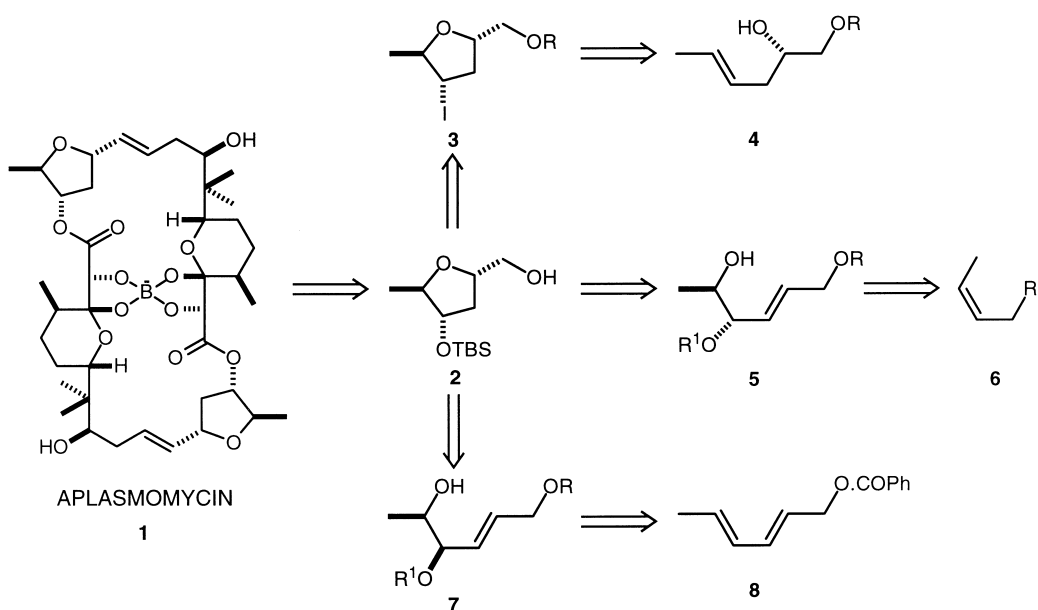
Keywords: Aplasmomycin; 5-*endo*; iodocyclisation; asymmetric; tetrahydrofuran.

In the foregoing paper,¹ we report that 5-*endo*-iodocyclisations of 3-alkene-1,2-diols are often very efficient and highly stereoselective. It occurred to us that such methodology could be useful in an expedient synthesis of the β -hydroxytetrahydrofuran **2**, a key component of the symmetrical, boron-containing bis-macrolide Aplasmomycin **1**.² We were especially keen to test our new methodology in this way, as previous approaches to this seemingly simple intermediate and related structures had necessitated at least 11 steps and in one route, many more.^{3–5}

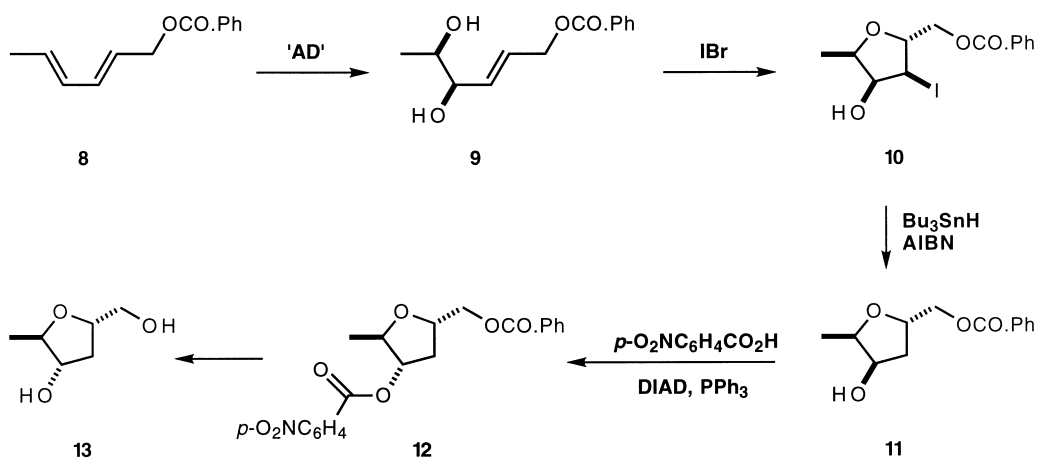
Our results provided us with a number of options. However, before examining these, we considered employing 5-*endo*-cyclisations of 4-alkene-1,2-diol derivatives **4** which we anticipated might lead to the β -iodotetrahydrofurans **3**, potential precursors to the target **2**. Such substrates are known to undergo exclusively 5-*exo*-cyclisations⁶ involving the distal 1-hydroxyl group. However, we felt that it might be possible to block this group as shown [i.e. **4**, R = SiR₃, R¹CO, etc.] and hence facilitate the desired 5-*endo* process. In the event, all such attempts failed; in each case, only 5-*exo* products⁶ were obtained, even when highly electron-deficient protecting groups such as trifluoroacetyl [**4**, R = COCF₃] were used. This was not a serious drawback, as it obviated the need for a potentially awkward and inefficient double inversion at the β -iodo centre, necessary in order to introduce the correct hydroxyl group stereochemistry, but did once again confirm the propensity of 5-*exo*-cyclisations to occur in preference to 5-*endo* processes when these are in direct competition.⁷

We therefore analysed the problem in terms of our new methodology,¹ leading to the conclusion that such cyclisations, specifically of (*E*)-3-alkene-1,2-diols (**5** or **7**), should give β -hydroxytetrahydrofurans having the correct 2,5-*trans* stereochemistry necessary to access the target **2**, given that such cyclisations were viable with substrates having a second, distal allylic oxygen function and that a suitable protecting group ('R' in **5** and **7**) could be found. Initially, iodocyclisations of

* Corresponding author.



the *anti*-alkene-1,2-diols **5** seemed the best option, as access to tetrahydrofuran **2** would require deiodination and protecting group manipulation. However, such precursors are not especially amenable to stereoselective assembly: routes via non-chelation controlled additions of acetylides to lactaldehydes give *anti:syn* ratios of around 85:15 at best⁸ while asymmetric dihydroxylation (AD) approaches would require the use of (*Z*)-alkene precursors **6** which often give poor levels of asymmetric induction.⁹ However, we were keen to utilise the excellent AD method which has resulted in the abbreviation of so many reaction sequences since its discovery. We reasoned that use of an (*E*)-alkene precursor would be preferable, as this would be expected to give very high levels of enantiomeric enrichment in the AD reaction; iodocyclisation of the resulting *syn*-alkene-1,2-diols **7** should also give the required 2,5-*trans* stereochemistry in the resulting tetrahydrofuran¹ but necessitate an additional β -hydroxyl inversion step. Despite this latter feature, we pursued this approach, especially because the Sharpless group have reported that the dienyl benzoate **8** undergoes highly regio- and enantioselective AD reactions.¹⁰

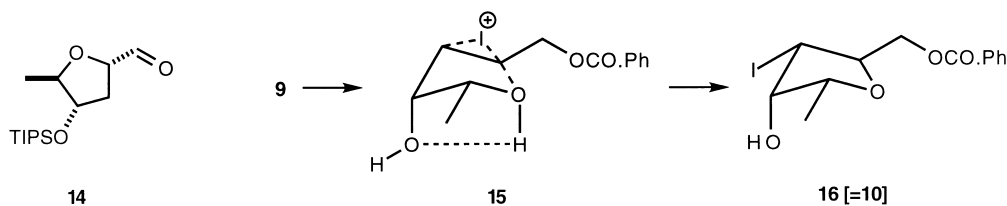


In the event, asymmetric dihydroxylation of dienyl benzoate **8** was highly regioselective when carried out at 0°C using 0.01 equiv. of (DHQD)₂-PHAL and 0.004 equiv. of K₂OsO₄ together with 3 equiv. each of potassium carbonate and potassium ferricyanide and 1 equiv. of MeSO₂NH₂ in 1:1 aqueous *t*-butanol.^{9,10}

The desired (*R,R*)-alkene-diol **9** was isolated after chromatography in 50–55% yields, with some losses resulting from benzoate hydrolysis during work-up. The material showed [α]_D +2.1 (*c* 2.10, CHCl₃) [lit.¹⁰ [α]_D +2.2 (*c* 2.00, CHCl₃)]; we thus assumed 98% ee, as reported by Sharpless et al.⁹

According to our model work,¹ iodocyclisation was expected to deliver the desired iodotetrahydrofuran with stereoselectivities in the range 4–6:1. Under the usual conditions (3 equiv. each of iodine and NaHCO₃ in dry acetonitrile, protected from light), cyclisation onto the relatively electron-poor alkene was slow, but after 72 h at ambient temperature, a good yield of an iodotetrahydrofuran was obtained as largely a single isomer according to ¹H NMR data. Further optimisation established better conditions in which 2 equiv. of iodine monobromide were used in place of elemental iodine, which resulted in complete cyclisation at –10°C during 16 h. The resulting product was obtained with an enhanced 14:1 ratio in favour of the desired isomer **10** which was secured in a pure state in 78% yield by fractional crystallisation, m.p. 78–80°C. Nuclear Overhauser experiments were inconclusive but the expected stereochemistry was confirmed by single crystal X-ray analysis.¹¹ Subsequent deiodination (Bu₃SnH, AIBN, C₆H₆, 80°C), which provided 70–75% isolated yields of the hydroxytetrahydrofuran **11**, was followed by Mitsunobu inversion¹² using diisopropyl azodicarboxylate, triphenylphosphine and *p*-nitrobenzoic acid.¹³ Problems in completely separating the resulting ester **12**¹⁴ from by-products were obviated by treating the crude mixture with catalytic methanolic sodium methoxide which, following chromatography, delivered the desired diol **13** in 78% isolated yield from these two steps.¹⁵ This showed [α]_D +45.1 (*c* 1.01, CHCl₃) [lit.³ [α]_D +45.7 (*c* 0.84, CHCl₃)], suggesting >95% optical purity, and previously has been converted into the corresponding aldehyde **14**, prior to homologation using a Julia condensation to establish the (*E*)-alkene function during introduction of much of the remainder of the target **1**.

The excellent level of stereocontrol observed in the key 5-*endo*-cyclisation may be due to intramolecular hydrogen bonding between the two hydroxy groups. On the reasonable assumption that the pendant methyl group adopts a pseudoequatorial position, allowing hydrogen bonding between the reacting hydroxyl group and the now pseudoaxial β -hydroxyl, as depicted in structure **15**, cyclisation would result in the major product **10**, at least initially in conformation **16**.



This example demonstrates the potential of such cyclisations and highlights the use of iodine monobromide as a useful alternative to molecular iodine. Work aimed at further developing this theme is underway.

Acknowledgements

We thank the EPSRC Mass Spectrometry Service, Swansea University for the provision of high resolution mass spectral data and the EPSRC and Cardiff University for financial support.

References

1. Bew, S. P.; Barks, J. M.; Knight, D. W.; Middleton, R. M. *Tetrahedron Lett.* **2000**, *41*, 4447.
2. Fenical, W. *Chem. Rev.* **1993**, *93*, 1673. For recent isolation work in this area, see: Stout, T. J.; Clardy, J.; Pathirana, I. C.; Fenical, W. *Tetrahedron* **1991**, *47*, 3511; Hemscheidt, T.; Puglisi, M. P.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Rios, J. L.; Clardy, J. *J. Org. Chem.* **1994**, *59*, 3467; Irschik, H.; Schummer, D.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 26; Schummer, D.; Schomburg, D.; Irschik, H.; Reichenbach, H.; Höfle, G. *Annalen* **1996**, 965.
3. Nakata, T.; Saito, K.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 6341 and 6345.
4. White, J. D.; Choudhry, S. C.; Kang, M. C. *Tetrahedron Lett.* **1984**, *25*, 3671; White, J. D.; Vedananda, T. R.; Kang, M.-c.; Choudhry, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105; Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469, and *Chem. Lett.* **1987**, 2097. For synthetic studies of Boromycin and related structures, see: Hanessian, S.; Delorme, D.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *Can. J. Chem.* **1983**, *61*, 634; White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Gray, B. D.; Kang, M. C.; Kuo, S.-C.; Whittle, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 790, and references cited therein; Berger, M.; Mulzer, J. *J. Am. Chem. Soc.* **1999**, *121*, 8393.
5. Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816; Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818.
6. Tamaru, Y.; Kawamura, S.-i.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 2885; Tamaru, Y.; Hojo, M.; Kawamura, S.-i.; Sawada, S.; Yoshida, Z.-i. *J. Org. Chem.* **1987**, *52*, 4062; Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204.
7. Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1998**, *39*, 8909, and references cited therein.
8. Alami, M.; Crousse, B.; Linstrumelle, G.; Mambu, L.; Larchevêque, M. *Synlett* **1993**, 217.
9. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
10. Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345.
11. We are very grateful to Drs. A. K. M. Malik and D. E. Hibbs, Cardiff University, for these data.
12. Mitsunobu, O. *Synthesis* **1981**, 1; *Comp. Org. Synth.* **1991**, *6*, 1 and 65; Hughes, D. L. *Org. React.* **1992**, *42*, 335.
13. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017; Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.
14. Some analytically pure material, m.p. 113–114°C, was obtained by fractional crystallisation from MeOH.
15. Full analytical and spectroscopic data have been obtained for all compounds reported.