Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2129–2131
Tetrahedron Letters

Stereoselective synthesis of (+)-boronolide

S. Vasudeva Naidu, Priti Gupta and Pradeep Kumar*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India

Received 18 November 2004; revised 13 January 2005; accepted 21 January 2005

Abstract—An efficient enantio- and stereocontrolled total synthesis of (+)-boronolide from valeraldehyde is described. The key steps include a Sharpless asymmetric dihydroxylation, a chelation controlled Grignard reaction followed by Sharpless asymmetric epoxidation and a ring closing metathesis.

α-Pyrones (5,6-dihydro-2*H*-pyran-2-ones) possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists due to their broad range of biological activities. Examples of such compounds include (+)-boronolide **1** and its deacetylated and dideacetylated derivatives **2** and **3** (Fig. 1). Boronolide **1** is an α,β-unsaturated C-12 lactone isolated from the leaves and branches of *Tetradenia fruticosa*[1] and from the leaves of *Tetradenia barberae*,[2] which have been used as local folk medicines in Madagascar and South Africa.[3] Deacetylated **2** and dideacetylated boronolide **3** have been obtained from *Tetradenia riparia*,[4] a Central African species typically employed by the Zulu as an emetic, which is an infusion of the leaf has also been reported to be effective against malaria. The relative stereochemistry of **1** was determined by X-ray analysis.[5] The *R*-configuration at the C-6 position was proposed by application of Hudson's lactone rule to the molecular rotation. Later, the stereochemistry at the C-6 position was confirmed by the chemical degradation.[2]

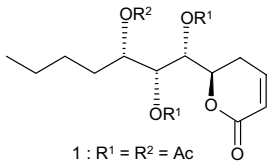


Figure 1.

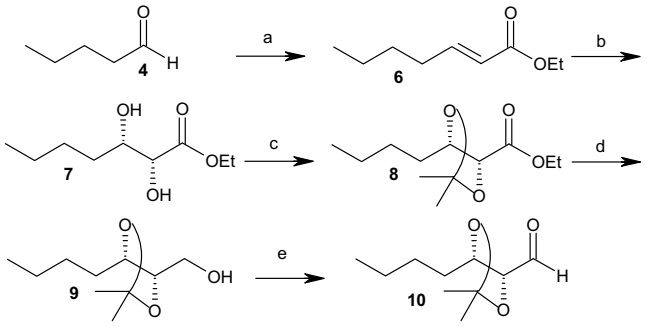
Various methods for the synthesis of (+)-boronolide **1** have been described in the literature.[6] The first synthesis of **1** was reported from an acrolein derivative[6a] in racemic form. Most of the enantioselective syntheses known for boronolide derive the asymmetry from chiral pool starting materials such as glucose,[6b] mannitol,[6e,i] tartaric acid,[6d,j] D-glucono-lactone[6j] and L-erythrulose,[6f] etc. However synthetic approaches involving achiral substrates as starting materials are rather scarce. One approach deals with the asymmetric aldol reaction of hydroxyacetyl furan and valeraldehyde using a novel dizinc catalyst.[6h] In another approach Honda et al.[6c] employed the Sharpless asymmetric dihydroxylation for the construction of all four contiguous asymmetric centres.

As a part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[7] and amino alcohols,[8] we have accomplished a stereoselective total synthesis of (+)-boronolide **1** from commercially available valeraldehyde employing a Sharpless asymmetric dihydroxylation, a chelation controlled vinyl Grignard reaction followed by a Sharpless asymmetric epoxidation and ring closing metathesis as the key steps.

According to the synthetic plan (Scheme 1), valeraldehyde was subjected to Horner–Emmons olefination with triethyl ester phosphonate **5** to furnish the (*E*)-α,β-unsaturated ester **6** in excellent yield. The ester **6** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions[9] to give the diol **7**[10] in 96% yield with 97% ee; $[\alpha]_D^{25}$ −8.8 (*c* 0.9, $CHCl_3$). Treatment of diol **7** with 2,2-dimethoxypropane in the presence of *p*-TSA gave the acetonide ester **8**, which on reduction

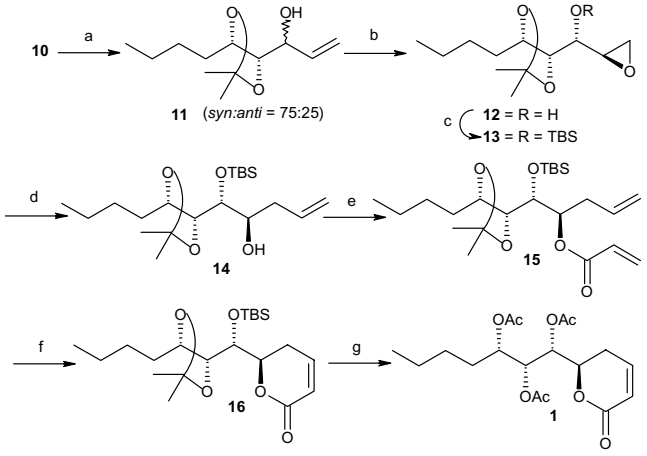
* Corresponding author. Tel.: +91 20 25893300x2050; fax: +91 20 25893614; e-mail: tripathi@dalton.ncl.res.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.120



Scheme 1. Reagents and conditions: (a) $Et_2P(O)CH_2CO_2Et$, **5**, LiBr, Et_3N, THF, rt, overnight, 89%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M in toluene), *t*-BuOH–H_2O (1:1), 0 °C, 24 h, 96%; (c) *p*-TSA, 2,2-DMP, CH_2Cl_2, 95%; (d) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 91%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C, 95%.

with DIBAL-H furnished the alcohol **9** in 91% yield. The alcohol **9** was subjected to oxidation under Swern conditions[11] to give the aldehyde **10** in excellent yield. To establish the third stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective vinylation (Scheme 2). Thus treatment of aldehyde **10** with vinylmagnesium bromide in THF in the presence of $MgBr_2{\cdot}Et_2O$ at −78 °C furnished the allylic alcohol **11** in 92% yield with moderate diastereomeric selectivity (dr = 75:25; *syn*:*anti*)[12a] as an inseparable mixture of diastereomers.[12b] Subsequently several attempts were made to achieve better selectivity with the use of additives such as $ZnCl_2$ or $TiCl_4$ and employing vinyl lithium as alkylating reagent with different solvent systems (CH_2Cl_2 or diethyl ether). However, the required *syn* selectivity could not be improved. The



Scheme 2. Reagents and conditions: (a) $CH_2{=}CHMgBr$, $MgBr_2{\cdot}Et_2O$, THF, −78 °C, 5 h, 92%; (b) Ti(OPr-*i*)$_4$, (+)-DIPT, *t*-BuOOH, dry CH_2Cl_2, −20 °C, 48 h, 78% (yield based on 75% of *syn* compound); (c) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, 0 °C to rt, 98%; (d) $CH_2{=}CHMgBr$, CuI, THF, −20 °C, 90%; (e) Acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to rt, 91%; (f) 10 mol% $(PCy_3)_2$-$Ru(Cl)_2{=}CH{-}Ph$, Ti(OPr-*i*)$_4$,CH_2Cl_2, reflux, 6 h, 89%; (g) (i) aq HF, CH_3CN, rt, 5 days, 65%; (ii) Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 88%.

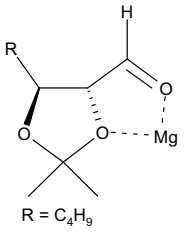


Figure 2.

formation of the major *syn*-diastereomer can be explained by the formation of the chelated five-membered transition state (Fig. 2).[13]

In order to generate the final stereogenic centre with an appropriate functionality, a Sharpless asymmetric epoxidation was employed in the next step. Thus, allylic alcohol **11** was treated with titanium tetraisopropoxide and *tert*-butyl hydroperoxide in the presence of (+)-DIPT under Sharpless asymmetric epoxidation conditions[14] to give the epoxide **12** in good yield and high diastereomeric excess (de = >95%) as judged by ^1H and ^{13}C NMR spectral analysis.[15] As expected the Sharpless kinetic resolution in the epoxidation reaction has a pronounced effect in enhancing the diastereomeric purity of the desired product. After protection of the hydroxyl group as the *tert*-butyldimethylsilyl ether, epoxide **13** was treated with vinylmagnesium bromide in the presence of a catalytic amount of CuI in THF at −20 °C to furnish the homoallylic alcohol **14** in excellent yield. Treatment of **14** with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate **15** in 91% yield. Olefin metathesis of **15** with commercially available Grubbs' first generation catalyst[16] (10 mol%) in the presence of Ti(OPr-*i*)$_4$ (0.3 equiv) in refluxing CH_2Cl_2 afforded the α,β-unsaturated-δ-lactone **16** in 89% yield. Finally, all the protecting groups in compound **16** were removed[6h] and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **1**. The physical and spectroscopic data of **1** were identical with those reported.[6h]

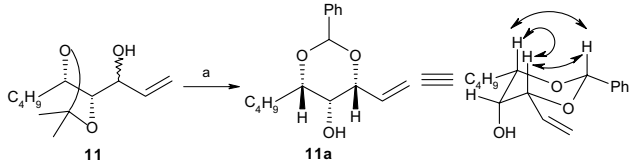
In conclusion, a practical and enantioselective total synthesis of (+)-boronolide has been achieved via Sharpless asymmetric dihydroxylation and a chelation controlled vinyl Grignard reaction followed by a Sharpless asymmetric epoxidation and ring-closing metathesis. The synthetic strategy described has significant potential for further extension to various isomers and other related α-pyrone derivatives. Currently, studies are in progress in this direction.

Acknowledgements

S.V.N. and P.G. thank CSIR and UGC New Delhi for financial assistance, respectively. We are grateful to Dr. M. K. Gurjar for his support and encouragement. The financial support from DST, New Delhi (Grant No. SR/S1/OC-40/2003) is gratefully acknowledged. This is NCL communication No. 6676.

References and notes

1. (a) Davies-Coleman, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1–35; (b) Adityachaudhury, N.; Das, A. K. *J. Sci. Ind. Res. (India)* **1979**, *38*, 265–277; (c) Siegel, S. M. *Phytochemistry* **1976**, *15*, 566–567.
2. Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1987**, *26*, 3047–3050.
3. Watt, J. M.; Brandwijik, M. G. B. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*; Livingston: Edinburgh, 1962; p 516.
4. (a) Van Puyvelde, L.; Dube, S.; Uwimana, E.; Uwera, C.; Domisse, R. A.; Esmans, E. L.; Van Schoor, O.; Vlietinck, A. *Phytochemistry* **1979**, *18*, 1215–1218; (b) Van Puyvelde, L.; De Kimpe, N.; Dube, S.; Chagnon-Dube, M.; Boily, Y.; Borremans, F.; Schamp, N.; Anteunis, M. J. O. *Phytochemistry* **1981**, *20*, 2753–2755.
5. Kjaer, A.; Norrestan, R.; Polonsky, J. *Acta Chem. Scand. Ser. B* **1985**, *39*, 745–750.
6. (a) Jefford, C. W.; Moullin, M.-C. *Helv. Chim. Acta* **1991**, *74*, 336–342; (b) Nagano, H.; Yasui, H. *Chem. Lett.* **1992**, 1045–1048; (c) Honda, T.; Horiuchi, S.; Mizutani, H.; Kanai, K. *J. Org. Chem.* **1996**, *61*, 4944–4948; (d) Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003–1006; (e) Chandrasekhar, M.; Raina, S.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4969–4972; (f) Carda, M.; Rodriguez, S.; Segovia, B.; Marco, J. A. *J. Org. Chem.* **2002**, *67*, 6560–6563; (g) Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 2317–2327; (h) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513–3516; (i) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039–4045; (j) Hu, S. G.; Hu, T. S.; Wu, Y. L. *Org. Biomol. Chem.* **2004**, *2*, 2305–2310.
7. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445–13450; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921–2923; (d) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149–6151; (e) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849–851.
8. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447–3449; (b) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426; (c) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309–10312; (d) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035–1037; (e) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957–1958; (f) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231–4232; (g) Kondekar, N. B.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5477–5479; (h) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877–5879.
9. (a) Becker, H.; Sharpless, K. B. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 448–451; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
10. For the measurement of enantiomeric excess, diol **7** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be >97% by chiral HPLC analysis (Chiralcel OD, petroleum ether–*i*-PrOH (98:2), 1 mL/min, 240 mm. Spectral data of compound **7**: colourless oil, $[\alpha]_D^{25}$ −8.8 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max} 3400, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.24–1.37 (m, 6H), 1.59 (t, J = 6.8 Hz, 3H), 3.20 (br s, 2H), 3.85 (dt, J = 6.8, 2.4 Hz, 1H), 4.06 (d, J = 2.4 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 13.8, 22.3, 27.6, 32.8, 61.4, 72.4, 73.2, 173.5. Anal. Calcd for $C_9H_{18}O_4$ (190.24): C, 56.82; H, 9.54. Found C, 56.61; H, 9.68.
11. For reviews on the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857–870; (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572.
12. (a) Compound **11** was subjected to acid treatment followed by 1,3-dihydroxy protection as the benzylidene derivative. The required isomer **11a** could easily be separated by silica gel column chromatography. The stereochemistry of compound **11** was unambiguously assigned based on NOE studies. Strong NOE correlations were observed between the 1,3-diaxial protons of the cyclic derivative **11a**. Reagents and conditions: (i) HCl, MeOH, rt, 12 h; (ii) $PhCH(OMe)_2$, *p*-TSA, CH_2Cl_2, rt, overnight; (b) Even after protection of the hydroxy group of **11** with the different protecting groups such as TBS, MOM, Ac and PMB, we were unable to separate the diastereomers by flash chromatography.



13. For reviews on Grignard reactions, see: *Chem. Rev.* **1999**, *99*, 1191–1223.
14. (a) Katasuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; (b) Baker, S. R.; Boot, J. R.; Molgan, S. E.; Osborne, D. T.; Ross, W. J.; Shrubsall, P. R. *Tetrahedron Lett.* **1983**, *24*, 4469–4472.
15. *Spectral data of compound* **12**: colourless oil, $[\alpha]_D^{25}$ −3.7 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max} 3453, 2956, 2931, 2893, 2859, 1379, 1254, 1192 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.1 Hz, 3H), 1.26–1.36 (m, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.46–1.66 (m, 3H), 2.09 (s, 1H), 2.77–2.89 (m, 2H), 3.22–3.28 (m, 1H), 3.68 (t, J = 7.1 Hz, 1H), 3.83–3.90 (m, 1H), 3.97–4.09 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.6, 27.0, 27.4, 28.2, 33.8, 44.4, 52.3, 71.5, 79.5, 81.3, 108.8. Anal. Calcd for $C_{12}H_{22}O_4$ (230.30): C, 62.58; H, 9.63. Found C, 62.71; H, 9.59.
16. For reviews on ring-closing metathesis see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830.