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Tetrahedron Letters 44 (2003) 5289–5292

TETRAHEDRON LETTERS

A concise and general methodology for the complete asymmetric synthesis of the orthogonally protected 2-amino-1,3,4-butanetriols (ABTs)

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Received 5 May 2003; revised 13 May 2003; accepted 14 May 2003

Abstract—A complete asymmetric synthesis of the orthogonally protected 2-amino-1,3,4-butanetriols **I** (ABTs: versatile four carbon chiral synthons) was accomplished via the regioselective asymmetric aminohydroxylation (AA) reaction and oxazoline chemistry in four to six steps from the starting olefin **1**. The *syn*-vicinal amino alcohol functionality of **I** was installed by the regioselective AA reaction of the achiral olefin **1** in a single step, and the *anti*-vicinal amino alcohol functionality of **I** was derived from the *syn*-amino alcohol **2** by inverting the C2 hydroxy group stereochemistry through the formation and hydrolysis of the oxazoline **7**. Thus, the present strategy represents the most efficient and general asymmetric synthesis of ABTs so far.

Enantiomerically pure vicinal amino alcohols constitute an important family of natural and man-made organic compounds.[1] Among them, of particular interest are the orthogonally protected 2-amino-1,3,4-butanetriols (ABTs) **I**, since they can provide versatile four carbon chiral building blocks for the asymmetric synthesis of a wide variety of biologically important organic compounds such as antiviral agents, anticancer agents, and antibiotics (Fig. 1).[2] As such, a number of methodologies have been developed for the asymmetric synthesis of ABTs.[3] In those methodologies, the vicinal amino alcohol functionality and stereochemistry of ABTs have been sequentially introduced by either the functional group manipulation of chiral starting materials or by the regio- and/or enantioselective ring opening reaction of epoxides and aziridines by nitrogen and oxygen nucleophiles respectively. In other approaches, Lewis acid mediated nucleophilic addition reaction of chiral nitrones[4] and enzymatic resolution reaction of racemic vicinal azido alcohols[5] have also been utilized for the asymmetric synthesis of ABTs.

Conceptually the most efficient methodology for the installation of the vicinal amino alcohol functionality and stereochemistry of ABTs would be via the Sharpless asymmetric aminohydroxylation (AA) reaction[6] of appropriate four carbon olefins. Thus, it is rather surprising to find that the AA reaction has never been utilized for the asymmetric synthesis of ABTs. This may be attributed to difficulty in controlling regiochem-

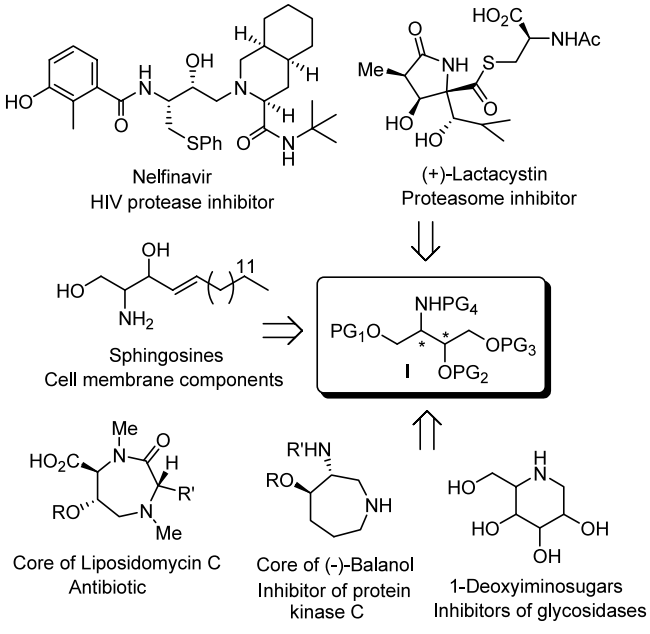

Figure 1.

Keywords: 2-amino-1,3,4-butanetriols; regioselective aminohydroxylation; Mitsunobu reaction; oxazoline.

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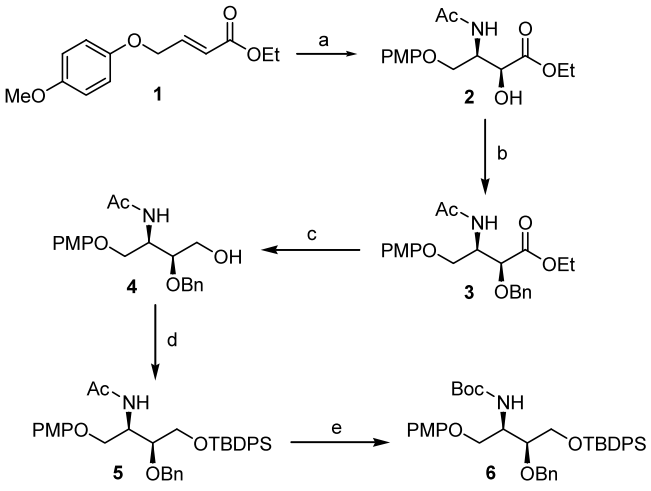
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01208-5

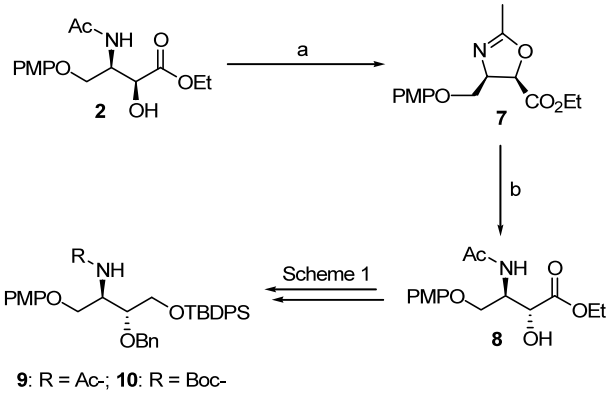
istry of the AA reaction of olefins. We recently developed a substrate-based methodology that allowed the regioselective control of the Sharpless asymmetric aminohydroxylation (AA) reaction of *trans*-disubstituted olefins.[7] In this approach, steric, electronic, and aryl–aryl stacking interactions between olefins and the AA catalyst were utilized to control regioselectivity. As our continuous effort to apply the *regioselective* AA reaction of olefins to the asymmetric synthesis of chemically and biologically important compounds,[8] herein we report an extremely succinct and stereoselective synthesis of the orthogonally protected ABTs. Also reported is a convenient methodology for the conversion of the *syn*-amino alcohols to the *trans*-amino alcohols through the two step one pot reaction involving the formation and hydrolysis of oxazolines. Therefore, the strategy presented here makes it possible to prepare all four stereoisomers of ABTs, and thus should provide a general and divergent methodology for the asymmetric synthesis of ABTs from the readily available achiral olefins.



Scheme 1. *Reagents and conditions*: (a) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 2:1, 4°C, 8 h, 70%; (b) NaH, BnCl, DMF, 0°C, 10 h, 78%; (c) $LiBH_4$, ether, 15 min, quantitative; (d) TBDPSCl, TEA, DMAP, CH_2Cl_2, 25°C, 4 h, 95%; (e) $(Boc)_2O$, DMAP, THF, 70°C, 4 h, then $NH_2NH_2{\cdot}H_2O$, MeOH, 25°C, 4 h, 90%.

Scheme 1 depicts our synthesis of the orthogonally protected *syn*-ABTs **5** and **6** starting from the achiral α,β-unsaturated ester **1**. The regioselective AA reaction of **1** afforded the *syn*-aminoalcohol **2** with an excellent regio- (>20:1) and enantioselectivity (>99%). The 4-(*p*-methoxy)phenoxy group of **1** plays a dual role in our synthesis: its aryl–aryl stacking interaction with the aryl groups of the AA catalyst can increase regio- and enantioselectivity of the AA reaction of **1** (role as a catalyst binder),[9] and it can also act as a convenient alcohol protection group (role as a protection group).[10] Protection of the hydroxyl group of **2** by benzyl chloride in presence of sodium hydride gave the benzyl ether **3**, which on reduction with lithium borohydride in the ether solution containing a trace amount of methanol turned into the alcohol **4**. Protection of the alcohol **4** by TBDPSCl/DMAP finished the concise asymmetric synthesis of the orthogonally protected *syn*-(2*R*,3*S*)-2-amino-1,3,4-butanetriol **5** in an overall 51.9% yield from the starting olefin **1**. The *N*-acetyl group of **5** was transformed to the more easily removable and manipulable *N*-*t*-butyloxycarbonyl (Boc) group by treating Boc anhydride and then hydrazine hydrate in methanol to produce **6**.[11]

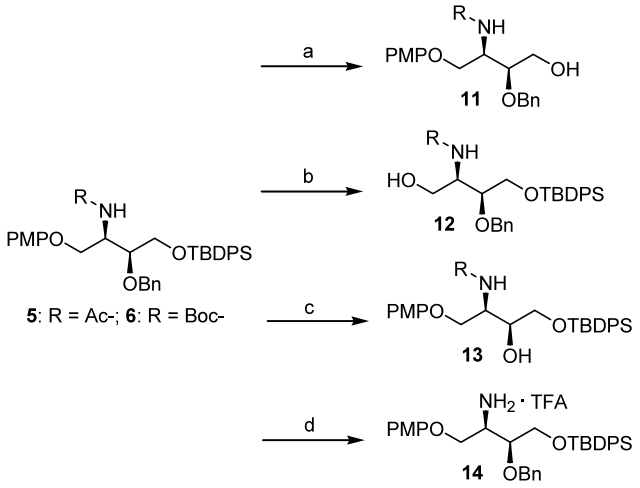
Asymmetric synthesis of the orthogonally protected *anti*-ABTs **9** and **10** required inversion of the C2 hydroxy group stereochemistry of the *syn*-amino alcohol **2**, and this was accomplished by using oxazoline chemistry (Scheme 2). Upon treatment of triphenylphospine and diisopropyl azadicarboxylate (DIPAD; Mitsunobu conditions),[12] **2** underwent an intramolecular cyclization to give the oxazoline **7**. Inspection of the coupling constant between the two vicinal hydrogens at C2 and C3 of **7** ($J=11.0$ Hz) proved that in fact the formation of the oxazoline **7** proceeded with inversion of the hydroxyl configuration at C2 of **2**.[12b,13] Mild acidic hydrolysis of **7** followed by the addition of potassium carbonate to bring pH of the reaction mixture to 9.0 furnished the *trans*-amino alcohol **8**.[14] Noteworthy is that two step conversion of **2** to **8** could be carried out in one pot. Application of the reaction sequence described in Scheme 1 transformed **8** to the *anti*-(2*R*,3*R*)-ABT **9** and **10**.



Scheme 2. *Reagents and conditions*: (a) Triphenylphosphine, diisopropyl azadicarboxylate, THF, 0°C, 1 h; 60%, (b) 0.3N HCl, THF, 20 min, then K_2CO_3, pH 9.0, 1 h, 90%.

Finally, orthogonality of the four protection groups in **5**, **6**, **9**, and **10** was tested by selectively unmasking each protection group. As expected, the TBDPS, PMP, Bn, and Boc groups could be selectively removed by TBAF, ceric ammonium nitrate (CAN), Pd/C and H_2, and 50% TFA in CH_2Cl_2 respectively (Scheme 3).

In summary, an extremely concise methodology for the asymmetric synthesis of the orthogonally protected *syn*- and *anti*-ABTs has been developed, which utilized the regioselective aminohydroxylation reaction of olefins and oxazoline chemistry. Furthermore, since the enantiomers of **5**, **6**, **9**, and **10** can be synthesized by using $(DHQ)_2PHAL$ ligand instead of $(DHQD)_2PHAL$ for



Scheme 3. *Reagents and conditions*: (a) TBAF, THF, 25°C, 1 h, 98%; (b) CAN, MeCN–H_2O (4:1), 0°C, 10 min, 85%; (c) Pd/C, H_2, MeOH, 96%; (d) TFA–CH_2Cl_2 1:1, 0°C, 20 min, 85%.

the regioselective AA reaction of **1**, the present strategy represents a general solution for the complete asymmetric synthesis of ABTs from the readily available achiral olefin **1**.[15] Total asymmetric synthesis of the molecules in Figure 1, which is employing the orthogonally protected ABTs as key synthetic intermediates, is currently underway, and will be reported in due course.

Acknowledgements

Financial support from National Institute of Health (GM 08194) and The Welch Foundation (AX-1534) is gratefully acknowledged.

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15. Spectroscopic data of selected new compounds. **5**: $[\alpha]_{589}=-51.56$ (*c* 1.35, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ: 7.683–7.660 (m, 4H), 7.451–7.428 (m, 2H), 7.403–7.367 (m, 4H), 7.36–7.298 (m, 5H), 6.862 (d, 2H, $J=9.0$ Hz), 6.832 (d, 2H, $J=9.0$ Hz), 5.885 (d, 1H, $J=9.0$ Hz), 4.669 (d, 1H, $J=12.0$ Hz), 4.587–4.540 (m, 1H), 4.493 (d, 1H, $J=12.0$ Hz), 4.030 (dd, 1H, $J=4.5$ and 9.0 Hz), 3.970 (ddd, 1H, $J=2.0$, 5.5 and 7.0 Hz), 3.866 (t, 1H, $J=9.0$ Hz), 3.800–3.766 (m, 4H), 3.723 (dd, 1H, $J=5.5$ and 11.0 Hz), 1.935 (s, 3H), 1.052 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.79, 153.92, 152.44, 137.95, 135.60, 135.56, 133.20, 132.97, 129.74, 129.71, 128.36, 128.05, 127.85, 127.71, 115.46, 114.62, 76.79, 73.54, 66.26, 63.33, 55.68, 48.81, 26.75, 23.26, 19.05; **6**: $[\alpha]_{589}=-42.92$ (*c* 1.3, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ: 7.687–7.672 (m, 4H), 7.453–7.425 (m, 2H), 7.397–7.368 (m, 4H), 7.284–7.227 (m, 5H), 6.843 (s, 4H), 5.024 (d, 1H, $J=9.0$ Hz), 4.655 (d, 1H, $J=11.0$ Hz), 4.473 (d, 1H, $J=11.0$ Hz), 4.305–4.255 (m, 1H), 4.025 (dd, 1H, $J=5.0$ and 9.0 Hz), 3.951–3.931 (m, 1H), 3.896 (t, 1H, $J=9.0$ Hz), 3.796–3.783 (m, 5H), 1.441 (s, 9H), 1.057 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.48, 153.88, 152.58, 138.12, 135.56, 133.30, 133.14, 128.28, 127.93, 127.70, 115.53, 114.62, 79.27, 77.07, 73.39, 66.85, 63.38, 55.70, 50.05, 28.34, 26.76, 19.11; **7**: ^1H NMR (500 MHz, $CDCl_3$) δ: 6.783–6.767 (m, 4H), 4.989 (d, 1H, $J=11.0$ Hz), 4.705–4.665 (m, 1H), 4.110–3.929 (m, 4H), 3.734 (s, 3H), 2.083 (s, 3H), 1.138 (t, 3H, $J=7.0$ Hz); **8**: $[\alpha]_{589}=-47.23$ (*c* 6.5, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ: 6.801 (s, 4H), 6.253 (d, 1H, $J=8.5$ Hz), 4.756–4.708 (m, 1H), 4.316 (d, 1H, $J=4.0$ Hz), 4.284–4.222 (m, 1H), 4.186–4.104 (m, 1H), 4.027 (dd, 1H, $J=5.0$ and 10.0 Hz), 3.967 (dd, 1H, $J=7.5$ and 10.0 Hz), 3.745 (s, 3H), 2.020 (s, 3H), 1.262–1.185 (m, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.28, 170.03, 154.17, 152.07, 115.40, 114.59, 70.62, 65.85, 62.00, 55.62, 50.56, 23.12, 13.91; **9**: $[\alpha]_{589}=-2.09$ (*c* 2.44, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ: 7.734–7.709 (m, 4H), 7.463–7.435 (m, 2H), 7.403–7.360 (m, 4H), 7.321–7.253 (m, 5H), 6.823 (d, 2H, $J=9.0$ Hz), 6.791 (d, 2H, $J=9.0$ Hz), 6.207 (d, 1H, $J=9.0$Hz), 4.693 (d, 1H, $J=12.0$ Hz), 4.583–4.545 (m, 1H), 4.522 (d, 1H, $J=12.0$ Hz), 4.150 (dd, 1H, $J=4.5$ and 9.5 Hz), 3.994–3.953 (m, 2H), 3.922 (dd, 1H, $J=2.5$ and 11.0 Hz), 3.779 (s, 4H), 1.863 (s, 3H), 1.111 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.71, 153.99, 152.52, 138.26, 135.63, 235.59, 132.95, 132.88, 129.84, 129.80, 128.35, 127.82, 127.79, 127.74, 127.63, 115.46, 114.61, 77.92, 72.43, 66.99, 64.75, 55.68, 49.52, 26.85, 23.28, 19.18; **10**: $[\alpha]_{589}=1.28$ (*c* 5.15, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ: 7.782–7.748 (m, 4H), 7.482–7.454 (m, 2H), 7.426–7.376 (m, 4H), 7.300–7.260 (m, 5H), 6.862 (d, 2H, $J=10.0$ Hz), 6.832 (d, 2H, $J=10.0$ Hz), 5.365 (d, 1H, $J=8.0$ Hz), 4.751 (d, 1H, $J=11.0$ Hz), 4.558 (d, 1H, $J=12.0$ Hz), 4.233 (d, 2H, $J=6.5$ Hz), 4.022–3.956 (m, 3H), 3.801 (s, 4H), 1.445 (s, 9H), 1.141 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.42, 153.92, 152.66, 138.30, 135.70, 135.58, 133.12, 133.00, 129.69, 128.27, 127.78, 127.70, 127.66, 127.48, 115.51, 114.59, 79.19, 78.34, 72.70, 67.49, 64.72, 55.65, 50.75, 28.29, 26.81, 19.10.