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(*R*)-2,3-Cyclohexylideneglyceraldehyde: a novel template for simple entry into both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans

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Abstract—Sharpless asymmetric dihydroxylation at the terminal olefin of benzoates **3a** and **3b**, using both AD-mix α and AD-mix β afforded only one diastereomer of diols **5a** and **5b**, respectively. Diols **5a** and **5b** were easily transformed into *cis*- and *trans*-2,5-disubstituted tetrahydrofurans **7** and **14**, respectively, which were subsequently converted into known compounds **12** and **19**.

2,5-Disubstituted tetrahydrofurans (THFs) constitute important structural and functional sub-units in various bioactive natural products including the rapidly expanding group of cytotoxic polyethers,[1a,b] polyether antibiotics,[1c,d] antitumour acetogenins,[2] etc. As a result, stereoselective construction of both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans has drawn considerable attention from synthetic chemists. Several strategies have been adopted in this pursuit, namely, cyclisation of 4-alkenols,[3a–e] 3-alkenols,[3f] epoxy alcohols,[3g] Ti-mediated coupling of acetylated γ-lactols or lactones with chiral enolates,[4] tandem 1,3-dipolar cycloaddition/electrophilic cyclisations supported on a polymer,[5] asymmetric [3+2]-annulation of chiral β-silyloxyallylsilanes,[6] cyclisation of 1,4-diols[7a,b] derived from several chiral templates, oxidative cyclization of 1,5-dienes,[7c] etc. Evidently, only a few of the reported approaches led to the formation of either *cis*-[3c,g,7c] or *trans*-2,5-disubstituted THFs.[3a,b,f,4a,b] In addition, it has been observed that many of these strategies have limitations such as moderate stereoselectivity in the crucial step and lengthy routes. Hence, the design and development of a simple and stereodivergent strategy to construct both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans (THF's) have assumed considerable importance in organic synthesis.

During our ongoing programme on the synthesis of bioactive molecules, we have exploited easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**)[8a] to construct several structural units, namely alkanetriols,[8a–d] ribofuranoses,[8c,e–g] γ-lactones,[8h] δ-lactones,[8i] which are widely prevalent in bioactive natural products. We present here another simple and efficient application of **1** as a novel template for stereodivergent entry into both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans.

Compound **1** was treated with the Grignard reagent of 4-bromobutene to produce **2** in good yield (81%) with *anti*-selectivity [*syn* **2a**[9]:*anti* **2b**[10] = 9.5:90.5]. As on previous occasions,[8] the diastereomers **2a**,**b** were easily separable by column chromatography. Compound **2a** could also be prepared stereoselectively following an oxidation–reduction strategy.[8d] Hence, PCC oxidation of a mixture of **2a** and **2b**, followed by K-Selectride reduction of the resulting ketone **4** yielded **2a** in excellent yield (95%) with almost absolute *syn* selectivity [*syn* **2a**:*anti* **2b** = 99.1:0.9]. Benzoylation of **2a** produced **3a**, which was subjected to Sharpless asymmetric dihydroxylation[11] separately with AD-mix α and AD-mix β. Interestingly, both these hydroxylations afforded only the diastereomeric diol **5a**[12] with absolute stereoselectivity. Monotosylation of **5a** regioselectively at the 1° hydroxyl produced **6** which on treatment with K_2CO_3 gave *trans*-2,5-disubstituted tetrahydrofuran **7**. Benzylation of **7** followed by deketalisation of the resulting THF **8** with aqueous CF_3COOH afforded diol **9**[13] in good yield. This was converted into epoxide **11** via monotosylation at the 1° hydroxyl and base treatment of tosylate **10**.

Keywords: (*R*)-2,3-Cyclohexylideneglyceraldehyde; Sharpless asymmetric dihydroxylation; Absolute stereoselectivity; 2,5-Disubstituted tetrahydrofurans; Substrate controlled addition; Stereodiversity.
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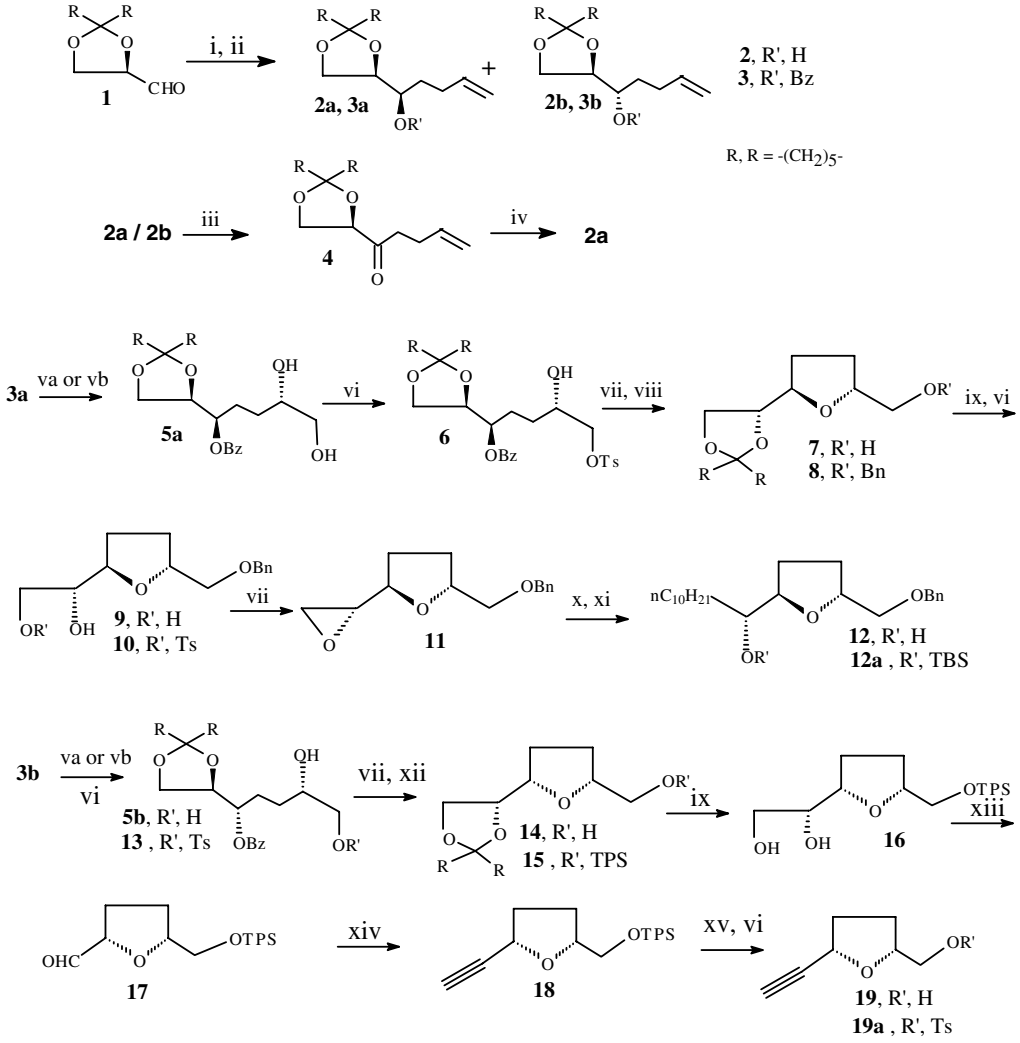
Cu(I)-Catalysed addition of *n*-nonylmagnesium bromide to **11** afforded the known alcohol **12**[6] (Scheme 1). The spectral and optical data of **12** prepared by us and its TBS derivative **12a** were in good agreement with those reported.[6,14]

Next, benzoate **3b** (derived from **2b**) was subjected to Sharpless dihydroxylation[11] by separate treatment with AD-mix α and AD-mix β. As with **3a**, both of these hydroxylations afforded the same diastereomeric diol **5b**[15] with absolute stereoselectivity. Monotosylation of **5b**, regioselectively at the 1° hydroxyl, produced **13**, which on treatment with K_2CO_3 afforded *cis*-2,5-disubstituted tetrahydrofuran **14**. Silylation of the hydroxyl and deketalisation of the resulting THF **15** with aqueous CF_3COOH afforded diol **16**[16] in good yield. $NaIO_4$ cleavage of the 1,2-diol unit of **16** yielded aldehyde **17** which was transformed into alkyne **18** following a known procedure.[17] This was desilylated on treatment with TBAF to afford the known *cis*-2,5-disubstituted-THF **19**[7b] (Scheme 1) as verified from spectral and optical data and also from the data of its tosyl derivative **19a** which were in good agreement with the reported data.[7b,18]

Thus, a stereodivergent and operationally simple strategy has been established to obtain both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans starting from the same substrate **1** employing Sharpless asymmetric hydroxylation reactions. The formation of only one diastereomer of diols **5a** and **5b** from **3a** and **3b** with either of the SAH reagents suggested that unlike in literature precedence,[11] in both cases, the dihydroxylation reactions were highly substrate controlled. Furthermore, it was evident that α-dihydroxylation took place in both SAH reactions with the benzoates **3a**,**b** irrespective of their having opposite stereochemistry at C-3. This suggested that the bulky cyclohexyl moiety, rather than



Scheme 1. Reagents and conditions: (i) 4-butenylMgBr, 0 °C–rt, THF, 81%; (ii) BzCl, Py, 0 °C, 96%; (iii) PCC, CH_2Cl_2, rt, 73%; (iv) K-Selectride, THF, −78 °C, 95%; (v) (a) ADmix-α, *t*-BuOH/H_2O (1:1), 0 °C, 82% for **3a**–**5a**; 86% for **3b**–**5b**; (v) (b) ADmix-β, *t*-BuOH/H_2O (1:1), 0 °C, 83% for **3a**–**5a**; 80% for **3b**–**5b**; (vi) *p*-TosCl, Py, 0 °C, 90% for **5a**–**6**; 87% for **9**–**10**; 83% for **5b**–**13**; 91% for **19-19a**; (vii) K_2CO_3, MeOH, rt, 92% for **6**–**7**; 86% for **10**–**11**; 89% for **13**–**14**; (viii) NaH, $PhCH_2Br$, THF, reflux, 90%; (ix) CF_3CO_2H, H_2O, 0 °C, 87% for **8**–**9**; 81% for **15**–**16**; (x) $nC_9H_{19}MgBr$, CuI, THF, −50 °C, 84%; (xi) TBDMSCl, Im, rt, 88%; (xii) TBDPSCl, Im, rt, 86%; (xiii) $NaIO_4$, CH_3CN–H_2O (3:2), rt, 84%; (xiv) (a) Zn, PPh_3, CBr_4, CH_2Cl_2, rt, 83%; (b) *n*BuLi, THF, − 78 °C, 83%; (xv) TBAF, THF, rt, 74%.

the –OBz, might play a role in directing the site of dihydroxylation by the AD-mix reagents at the terminal olefins. However, with hindsight this proved advantageous to attain stereodiversity in this strategy to construct both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans starting from two diastereomeric alcohols originating from **1**.

References and notes

1. (a) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, 1043–1044; (b) Kang, S. H.; Lee, S. B. *Chem. Commun.* **1998**, 761–762; (c) O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205; (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3–72.
2. (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540; (b) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423–430; (c) Hoppe, R.; Scharf, H. D. *Synthesis* **1995**, 1447–1464; (d) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–308.
3. (a) Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416–2423, and references cited therein; (b) Zhang, H.; Mootoo, D. R. *J. Org. Chem.* **1995**, *60*, 8134–8135; (c) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964; (d) Miura, K.; Hondo, T.; Okajima, S.; Hosomi, A. *Eur. J. Org. Chem.* **2006**, 3251–3258; (e) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1799–1803; (f) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 1955–1958; (g) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627–628.
4. (a) Jalce, G.; Seck, M.; Franck, X.; Hocquemiller, R.; Figadere, B. *J. Org. Chem.* **2004**, *69*, 3240–3241; (b) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53–56.
5. Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061–10062.
6. Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035–8046.
7. (a) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819–4822; (b) Sharma, G. V. M.; Punna, S.; Prasad, T. R.; Krishna, P. R.; Chorghade, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1113–1123; (c) Goksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433–3436, and references cited therein.
8. (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587; (b) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104–6107; (c) Chattopadhyay, A.; Dhotare, B.; Hassarajani, S. A. *J. Org. Chem.* **1999**, *64*, 6874–6878; (d) Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571–2575; (e) Dhotare, B.; Chattopadhyay, A. *Synthesis* **2001**, 1337–1340; (f) Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett.* **2006**, *47*, 4701–4705; (g) Chattopadhyay, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2727–2730; (h) Chattopadhyay, A.; Dhotare, B. *Tetrahedron Lett.* **2005**, *46*, 3103–3105; (i) Dhotare, B.; Goswami, D.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 6219–6221.
9. Compound **2a**: $[\alpha]_D^{25}$ 7.2 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.4–1.6 (m, 12H), 1.94 (br s, 1H), 2.0–2.3 (m, 2H), 3.4–3.5 (m, 1H), 3.75 (m, 1H), 3.9–4.0 (m, 2H), 5.0–5.1 (m, 2H), 5.7–6.0 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.57, 23.80, 24.93, 29.50, 32.59, 34.66, 36.09, 65.54, 71.43, 78.55, 109.72, 114.79, 137.93. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.79. Found: C, 68.80; H, 9.91.
10. Compound **2b**: $[\alpha]_D^{25}$ 13.6 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.6 (m, 12H), 1.96 (br s, 1H), 2.0–2.3 (m, 2H), 3.7–3.8 (m, 1H), 3.9–4.1 (m, 3H), 5.0–5.1 (m, 2H), 5.7–6.0 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.61, 23.80, 24.97, 29.78, 31.73, 34.66, 35.9, 64.30, 70.16, 78.14, 109.39, 114.93, 137.90. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.79. Found: C, 69.15; H, 9.61.
11. Kolb, H. C.; Van Nieuwennhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
12. Compound **5a**: $[\alpha]_D^{25}$ 12.35 (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.6 (m, 12H), 1.8–1.9 (m, 2H), 2.34 (br s, 2H), 3.40 (dd, $J = 7.5$, 4.2 Hz, 1H), 3.5–3.9 (m, 3H), 4.03 (t, $J = 6.8$ Hz, 1H), 4.30 (m, 1H), 5.23 (m, 1H), 7.39–7.56 (m, 3H), 8.04 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.68, 23.78, 24.97, 27.13, 28.86, 34.72, 35.71, 65.12, 66.35, 71.86, 74.11, 77.88, 109.98, 128.29, 129.60, 129.88, 132.99, 166.36. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.77; H, 7.90.
13. Compound **9**: $[\alpha]_D^{23}$ −1.0 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.5–1.8 (m, 2H), 1.9–2.0 (m, 2H), 2.47 (br s, 2H), 3.4–3.5 (m, 3H), 3.65 (m, 2H), 3.9–4.0 (m, 1H), 4.1–4.2 (m, 1H), 4.57 (s, 2H), 7.27 (bm, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.69, 28.41, 63.99, 72.53, 73.10, 73.70, 78.13, 79.85, 127.47, 127.54, 128.18, 137.86. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.86; H, 7.78.
14. Compounds **19a** and **SI**–**V** of Ref. 6.
15. Compound **5b**: $[\alpha]_D^{25}$ 8.54 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.6 (m, 12H), 1.7–2.0 (m, 2H), 2.9 (br s, 2H), 3.35–3.45 (m, 1H), 3.56–3.69 (m, 2H), 3.89 (t, $J = 6.4$ Hz, 1H), 4.02–4.12 (m, 1H), 4.22 (m, 1H), 5.24 (t, $J = 4.2$ Hz, 1H), 7.2–7.5 (m, 3H), 8.10 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.58, 24.79, 27.19, 28.47, 34.52, 35.72, 65.30, 66.30, 71.72, 73.96, 76.27, 109.98, 128.19, 129.44, 129.64, 132.95, 165.98. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.08; H, 7.59.
16. Compound **16**: $[\alpha]_D^{25}$ −2.8 (*c* 1.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.8–2.0 (m, 4H), 2.90 (br s, 2H), 3.5–3.7 (m, 5H), 3.9–4.1 (m, 2H), 7.38 (m, 6H), 7.68 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.99, 26.60, 27.07, 27.22, 63.58, 65.65, 73.15, 79.41, 80.53, 127.49, 129.43, 129.51, 133.02, 133.32, 135.37. Anal. Calcd for $C_{20}H_{32}O_6Si$: C, 68.96; H, 8.05. Found: C, 68.75; H, 7.95.
17. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
18. Compounds **49** and **50** of Ref. 7b.