Pergamon

Tetrahedron Letters 41 (2000) 7863–7867

TETRAHEDRON LETTERS

From cycloolefins to chiral, polyfunctionalized linear C_6/C_{12} building blocks—biocatalysis, (−)-conduramine E

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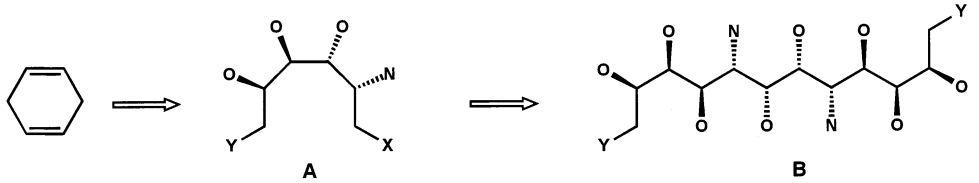
Received 3 August 2000; accepted 12 August 2000

Abstract

1,4-Cyclohexadiene is the starting material for the expeditious synthesis of the 1*S*2*S*3*S*4*R*- and 1*R*2*R*3*R*4*S*-epoxy-cyclohexene-1,4-diol monoacetates through enzyme-catalyzed hydrolysis and transesterification, respectively. The absolute configurations are established by correlation of (−)-**10** and known (+)-conduramine E. Ozonation and functional group manipulation open access to fully protected, polyfunctionalized C_6-aldehydes whose reductive coupling to C_2-symmetrical C_{12} building blocks is being explored. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: biocatalysis; conduramines; reductive dimerization.

As part of our long standing program—utilisation of bulk chemicals for the synthesis of chiral, polyfunctionalized, cyclic and linear, $C_6/C_8/C_{12}$ building blocks (trisanhydro-inositols,[1] inosadiamines,[2] diaminopolyols,[3,4] linear triepoxides,[5] linear 1,4-diamino-2,3-diols,[6] oxepanes, azepanes[4])—the construction of optically pure, polyfunctionalized C_6/C_{12} structures of type **A** and **B** from 1,4-cyclohexadiene has been explored.[7]



In earlier studies expeditious protocols for the large-scale preparation of the *meso*-configurated diacetoxy-epoxy-cyclohexenes **1** and **4**, and the respective diols **2** and **5** starting from 1,4-cyclohexadiene have been worked out.[1] In a screening process[8] with **1**, the commercial enzymes PLE (3 h, ee>95, 92%), PPL (ee = 93, 89%)[9] and SP 523 (ee = 94, 80–90%)[10] provided the same monoacetate (+)-**3** (1*S*2*S*3*S*4*R*) with preparatively useful selectivity, yields and

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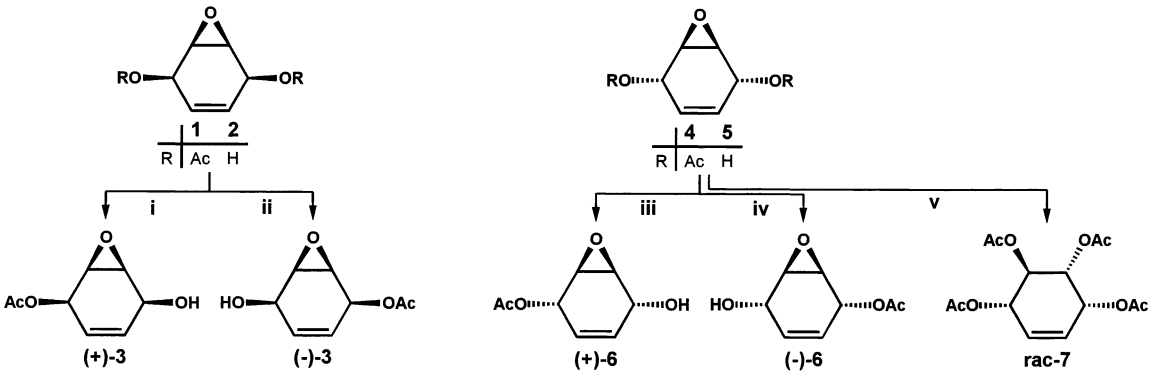
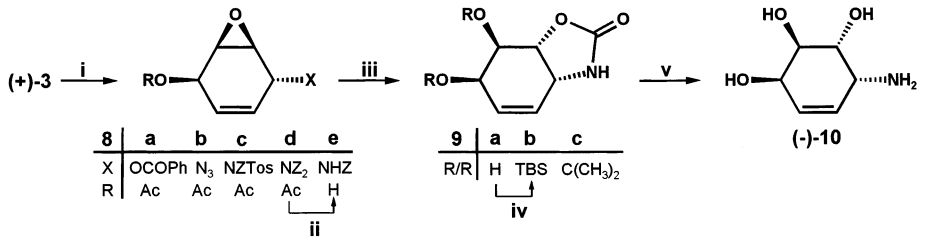
PII: S0040-4039(00)01395-2

reaction rates (5 h, 0.1 molar scale).[11] For the esterification of diol **2** with vinylacetate PPL and Lipozyme IM delivered (–)-**3** (1*R*2*R*3*R*4*S*) with comparably good results (ee ≥ 99, 60%, ee 96, 92%, 0.5 mmolar scale). With the *anti*-diacetate **4**, as well as the diol **5** under the same set of conditions the results were, however, not satisfactory: with AL AY30 and **4** monoacetate (+)-**6** was generated in high yield but only low enantioselectivity (ee = 60, 90%); a complication with **4** was its hydrolysis in the reaction medium to give with anchimeric assistance conduritol F – diacetate (90%) fully characterized as tetraacetate **rac-7**.[12] Exemplary for the generally unacceptably slow transesterifications of **5** is the outcome with AL AY30 (13 days, ee = 63, 35%). The absolute configuration of the monoesters (+)-**3** and (–)-**3** was ultimately established through correlation with (+)-conduramine E (see Scheme 1).



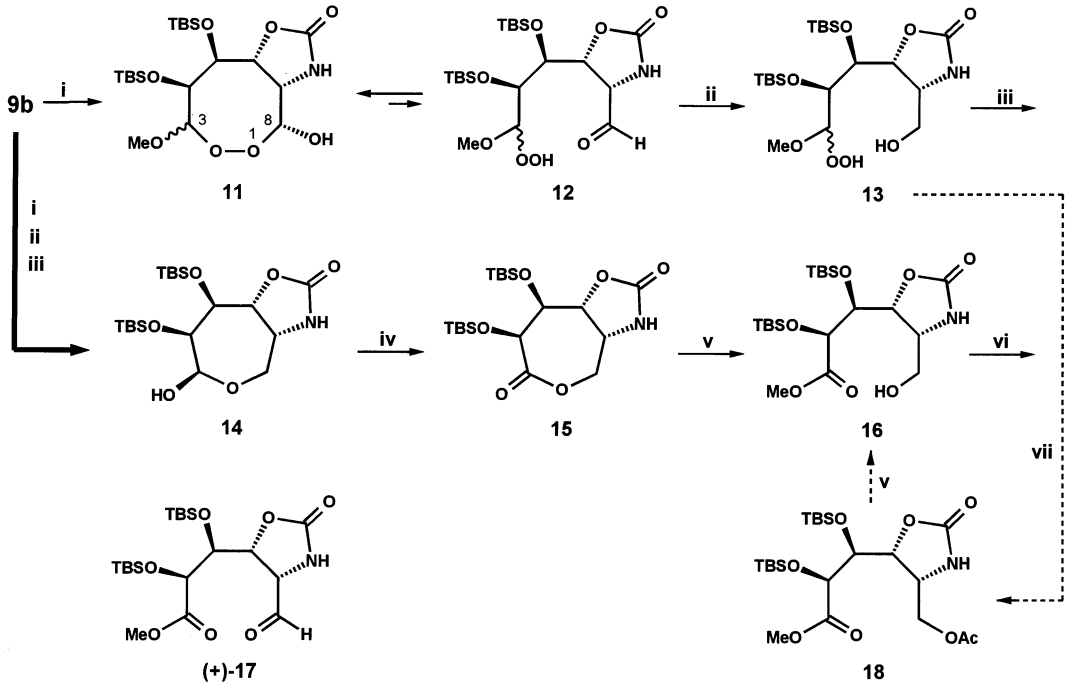
Scheme 1. (i) *n*-Hexane, 0.2N pH 7 phosphate buffer, SP 523 (4% w/w), room temp. (ii) TBME – vinylacetate, Lipozym IM (5% w/w), room temp. (iii) *n*-Hexane, pH 7 phosphate buffer, AL AY30 (10% w/w), 5 h, room temp. (iv) TBME – vinylacetate, AL AY30 (10% w/w), room temp. (v) pH 7 phosphate buffer, 3 days, room temp., then Ac_2O, Et_3N, DMAP, 70%

The installation of the amino-function as defined in **A** was pursued through substitution of the OH-group in hydroxy-acetate **3**. To avoid the complications encountered in the mesylation (tosylation), Mitsunobu conditions were applied.[13] With the four *O*- and *N*-nucleophiles shown, the products **8a–d** were isolated in good to high yields; the loss of material is in part ascribed to the competitive substitution by hydrogenated DEAD.[13] Specifically allylic azide **8b** equilibrated with its Cope isomer (1.2:1) after heating in $CDCl_3$ for 9 h at 60°C. For the preparation of **9b** as starting material for the sequence shown in Scheme 3, **8d** was quantitatively transformed into **8e**. Standard conditions neatly effected the *endo*-cyclisation to give urethane **9a**.[14] Mild hydrolytic conditions transformed **9a** into the so far unreported (–)-conduramine (–)-**10** ($[\alpha]_{25}^{D} = -225.8°$, $c = 1.5$, MeOH; (+)-conduramine E $[\alpha]_{25}^{D} = +239.7°$, $c = 1.7$, MeOH[15]) (Scheme 2).



Scheme 2. (i) Nucleophile (HO_2CPh, $(PhO)_2PON_3$, HNZTos, HNZ_2), PPh_3, DEAD, THF, room temp., 80–92%. (ii) NH_3–MeOH, room temp., quant. (iii) AcOH, H_2O, 110°C, 92%. (iv) TBS–Cl, imidazole, DMF, room temp. 80%. (v) $Ba(OH)_2$, 50°C, 86%

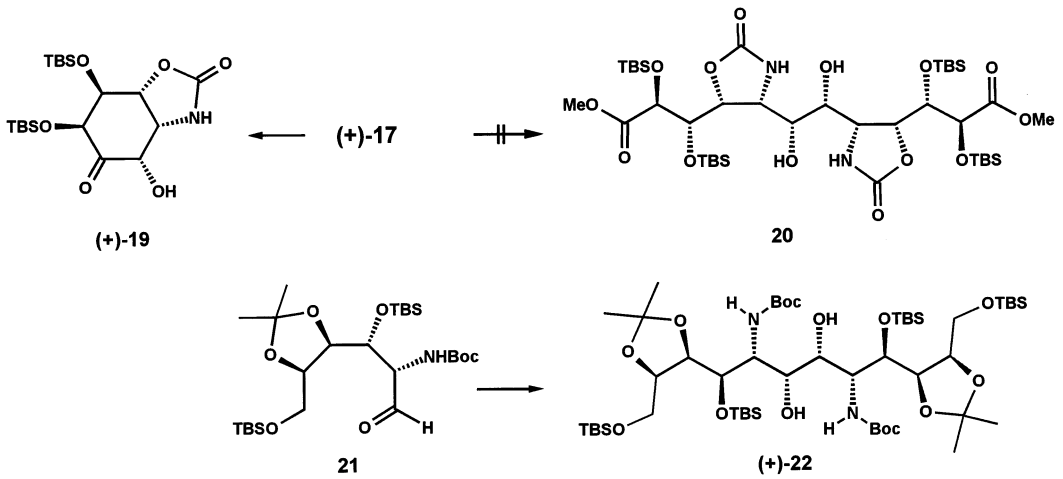
With aldehyde **17** as target, a monomer unit of type **A** with all other positions being protected for the reductive dimerization into **B**, bis-TBS-protected **9b** was exposed to ozone until total conversion (bluish colour). TLC and ^{1}H NMR control confirmed the nearly quantitative generation of a circa 3:1 mixture of 1,2-dioxocane **11** and linear hydroperoxy-aldehyde **12** (both circa 1:1 mixture of epimers)—besides traces of unknown structure. After standard work-up ($NaBH_4$, 2.5 molar equiv.) a 1:1 mixture of non-crystalline solids was isolated and separated for chromatographic characterization: the structures as **13** (36%, epimers) and oxepane **14** (44%) made it clear that the latter had originated from **13** after reduction and loss of methanol-**13** upon treatment with triethylamine quantitatively transformed into **14**. In practice, oxepane **14** is economically prepared from **9b** without isolation of any intermediate in a reproducible total yield of 90–95%. Of several reagents tested, TEMPO proved to be the one of choice for the oxidation lactol **14**→lactone **15**, readily converted to **16** with $MeOH/K_2CO_3$. The critical oxidation of **16** to α-amino-aldehyde (+)-**17** was, after extensive experimentation, achieved with full retention of stereochemistry along the Dess–Martin procedure,[16] if only in moderate yield. The alternative to proceed from **13** to **16** via **18** proved disadvantageous in view of the limited yield of **13** (Scheme 3).



Scheme 3. (i) O_3, CH_2Cl_2/MeOH (5/1), $NaHCO_3$, −78°C, >95%. (ii) $NaBH_4$, −78 to −20°C. (iii) Et_3N, 4°C, 90–95% from **9b**. (iv) TEMPO, nBu$_4$NBr, mCPBA, CH_2Cl_2, 0°C, quant. (v) K_2CO_3, MeOH, room temp., quant. (vi) Periodinane, CH_2Cl_2, room temp., 68%. (vii) Ac_2O, Et_3N, room temp., quant.

Intensive efforts directed at the V^{II}-mediated pinacol-homocoupling[17] of (+)-**17** to give **20** have not been successful; the protection pattern proved not compatible with these reaction conditions. Cyclohexanone (+)-**19** was isolated (50%) from a complex mixture of products. In a parallel study[7] this roadblock was circumvented by constructing C_6-aldehydes with better adapted protection measures. Thus from **21**, prepared from conduramine **9c** via a multistep sequence

(total yield 24%), C_2-symmetrical, solid C_{12} diamino-decaol (+)-**22** was secured in good yield (70–75%); no stereoisomer of (+)-**22** could be detected (Scheme 4).



Scheme 4.

Acknowledgements

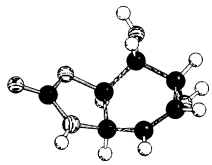
This project has been supported by the Deutsche Forschungsgemeinschaft. We thank F. Lay for competent technical assistance, Dipl.-Chem. H. Glatz for explorative experimentation, Dr. D. Hunkler and Dr. J. Wörth for NMR and MS spectra and Dr. L. Knothe for help with the manuscript.

References

1. (a) Schwesinger, R.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 942; (b) Prinzbach, H.; Keller, R.; Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 633; (c) Keller, R.; Schwesinger, R.; Fritsche, W.; Schneider, H.-W.; Hunkler, D.; Prinzbach, H. *Chem. Ber.* **1979**, *112*, 3347.
2. Schubert, J.; Keller, R.; Schwesinger, R.; Prinzbach, H. *Chem. Ber.* **1983**, *116*, 2524–2545.
3. Grabowski, S.; Armbruster, J.; Ruch, T.; Prinzbach, H. *Tetrahedron Lett.* **1997**, *38*, 5485–5488.
4. Armbruster, J.; Stelzer, F.; Landenberger, P.; Wieber, C.; Hunkler, D.; Keller, R.; Prinzbach, H. *Tetrahedron Lett.* **241**, *41*, 5483–5487.
5. Kammerer, J.; Rihs, G.; Prinzbach, H. *Angew.Chem., Int. Ed. Engl.* **1990**, *29*, 1038.
6. Armbruster, J.; Grabowski, S.; Ruch, T.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2242–2245.
7. Spielvogel, D. Dissertation, University of Freiburg, 27867.
8. List of enzymes: (a) Novo Nordisk: SP 523 (Novozym 398), SP 524 (Novozym 388), SP 525 (Novozym 525), SP 526 (Novozym 868), Novozym 435, Lipozym IM; (b) Amano: A 6, AP 6, AY30, CE 5, D 20, F-AP 15, G 50, GC 4, L 5, M 10, N conc., PS, R 10; (c) Fluka: PPL; (d) Boehringer Mannheim: PLE.
9. Kammerer, J. Dissertation, University of Freiburg, 1990.
10. Carrera, G.; Riva, S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2226-2254, and references cited therein.
11. All new compounds have been fully characterized by elemental analysis (or HRMS) and spectra (IR, ^{1}H, ^{13}C, NMR, MS).—e.g. **22**: mp: 53°C (CH_2Cl_2), $[\alpha]_{21}^{D}=+39.0°$ ($c=2.8$, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=5.58$ (d, NH), 4.20–4.11 (m, 2H, 11H, 4H, 9H), 4.01 (dd, 3H, 10H), 3.90 (s, 6H, 7H), 3.74 (dd, 1aH, 12aH), 3.58 (dd,

1bH, 12bH), 3.57 (s, OH), 3.42 (dd, 5H, 8H), 1.41 (s, Me), 1.39 (s, Si^{t}Bu), 1.28 (s, Me), 0.11 (s, SiMe), 0.10 (s, SiMe), 0.09 (s, SiMe), 0.09 (s, SiMe); $J_{1a,1b}=J_{12a,12b}=11.0$, $J_{1a,2}=J_{11,12a}=4.3$, $J_{1b,2}=J_{11,12b}=5.8$, $J_{2,3}=J_{10,11}=5.2$, $J_{3,4}=J_{9,10}=9.1$, $J_{4,5}=J_{8,9}=4.9$, $J_{5,NH}=J_{8,NH}=9.2$ Hz; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=155.4$ (C=O), 107.3 ($C_{q\text{-acetonide}}$), 79.1 ($C_{q\text{-Boc}}$), 78.5 (C-3, C-10), 77.2 (C-2, C-11), 72.8 (C-4, C-9), 69.9 (C-6, C-7), 62.9 (C-1, C-12), 53.0 (C-5, C-8), 28.6 (^{t}Bu), 27.9 (Me), 26.3 (SiCH(CH_3)), 26.2 (SiCH(CH_3)), 25.6 (Me), 18.8 (SiCH(CH_3)), 18.6 (SiCH(CH_3)), −3.9 (SiMe), −4.5 (SiMe), −5.3 (SiMe), −5.3 (SiMe); MS (CI–NH_3): 1100.0 (10), 1099.0 (24), 1098.0 (45), 1097.0 (38) $[M]^+$, $[M+H]^+$, 141.0 (23), 999.0 (51), 998 (82), 997 (100); ESI-MS: $m/z=1137.8$ (4), 1136.8 (5), 1135.8 (7) $[M+K]^+$, 1122.9 (14), 1121.8 (44), 1120.9 (77), 1119.8 (100) $[M+Na]^+$, 1100.9 (17), 1099.9 (41), 1098.9 (70), 1097.8 (93) $[M]^+$, $[M+H]^+$; $C_{52}H_{108}N_2O_{14}Si_4$ (1097.8): calc. C, 56.89; H, 9.91; N, 2.55; found: C, 56.89; H, 9.65; N, 2.32.

12. Le Drian, C.; Vionnet, J.-P.; Vogel, P. *Helv. Chim. Acta* **1990**, *31*, 161–168.
13. Mitsunobu, O. *Synthesis* **1981**, 1–28.
14. Crystallographic data for **9a** (Schakal plot) have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK. Copies of the data can be obtained free of charge (e-mail: deposit@chemcrys.cam.ac.uk) on quoting the deposition number CCDC 147577. Efforts to prove the absolute configuration by anomalous X-ray diffraction have remained futile.



15. Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737–8740.
16. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *48*, 4155–4156.
17. Kammermeier, B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H. *Chem. Eur. J.* **1996**, *2*, 307–315.