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SYNTHESIS OF AXIALLY DISSYMMETRIC 3,5-OCTADIENE FRAMEWORK WITH C_2 CHIRALITY VIA PALLADIUM(II)-CATALYZED TWOFOLD [3,3]SIGMATROPIC REARRANGEMENT

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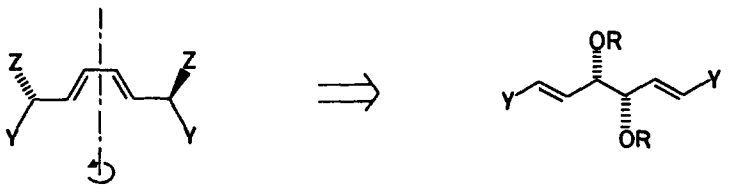
Summary: Palladium(II)-catalyzed [3,3]sigmatropic rearrangement of (4*R*,5*R*)-4,5-(bisacetoxy)-1,8-(bisbenzyloxy)-2(*E*),6(*E*)-octadiene has proceeded convergently to give (2*S*,7*S*)-2,7-(bisacetoxy)-1,8-(bisbenzyloxy)-3(*E*),5(*E*)-octadiene, translating the original chirality completely to the migration termini, which constitutes a novel synthesis of optically pure 3,5-octadiene with C_2 chirality.

Asymmetric Diels-Alder strategy is the most efficient and versatile entry for the synthesis of optically active cyclohexane ring systems containing multiple chiral centers. For performing it, a reasonable chiral auxiliary must be singly tagged in dienes or dienophiles, or both of them. Though creating new chiral centers by this method seems to be highly challenging, a progress in the breadth of cycloaddition processes and the level of efficiency in this context have extremely been encouraging.[1] Embarking on this field, we have contemplated to explore a novel asymmetric Diels-Alder system which features dienes possessing two chiral auxiliaries and, thereby, homotopic faces as well, and, consequently, only *endo* or *exo*-approach of dienophiles can be taken into account. A primary goal of this idea should be a replenishing supply of such novel dienes. In this communication we will disclose the realization of the goal, *i.e.*, synthesis of **1** in an optically pure form and in a multigram quantity relying on palladium(II)-catalyzed twofold [3.3]sigmatropic rearrangement[2] of 4,5-(bisacetoxy)-2,6-octadiene system (**2**) which is attainable from L-tartaric acid.

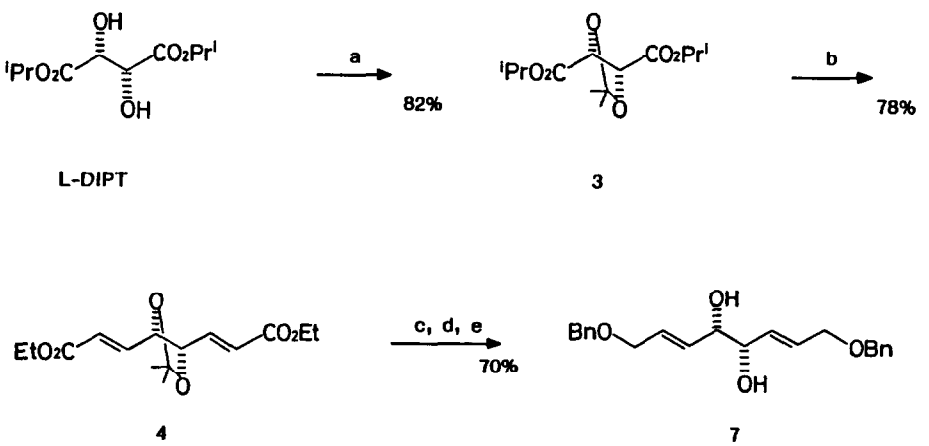


1 2

The first task to be achieved is to devise methodology for transforming L-tartaric acid into 4,5-(bishydroxy)-2,6-octadiene backbone in which *E*-geometry for both olefinic linkages is established. For this purpose we planned a simultaneous condensation of two terminal formyl functionalities which can be elaborated through simultaneous reduction of homotopic ester groups in appropriately protected L-tartaric acid diester with DIBAL-H. After long-standing endeavors toward this end we have found that selection of at least four factors, *i.e.*, the hydroxyl protecting group, the alkyl group of tartrate, the solvent, and the kind of condensation reagent, must be satisfied. Eventually, not MOM, TBDMS, or MEM but acetonide, not methyl or ethyl but isopropyl, not THF, CH_2Cl_2, or ether but toluene-

hexane system, and not Ph_3P=CHCOOEt but $(i\text{-PrO})_2P(O)CH_2COOEt$, respectively, have proven to be promising and reproducible.

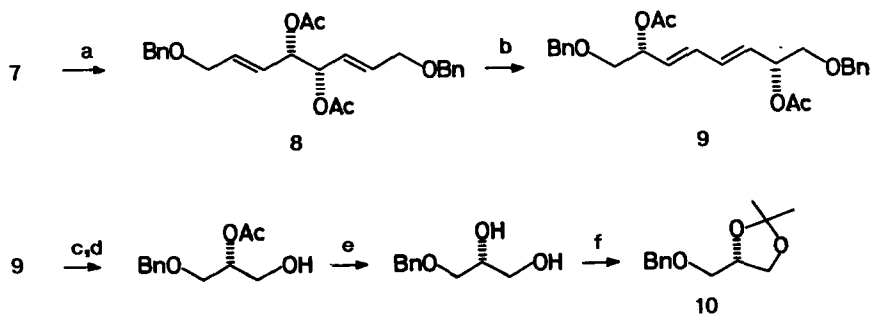
In the event diisopropyl L-2,3-*O*-isopropylidenetartrate (**3**) prepared from commercially available L-DIPT was reduced with DIBAL-H in toluene-hexane system at -78° and, at the same temperature, a solution of ethyl sodiodiisopropylphosphonoacetate in THF was introduced into the cold reaction, the condensation reaction being continued during 0.5 hour at -78° and additional 2 hours at -78° to 0°. The reaction was quenched by the addition of water and the product was chromatographically purified to give rise to diethyl (4*R*,5*R*)-4,5-*O*-isopropylidene-2(*E*),6(*E*)-octadiendioate (**4**) in 78% yield.[3]: $[\alpha]_D^{27}$ -70.1° (c 2.4, $CHCl_3$). For successful execution of this transformation the acetonide protecting group is essential, otherwise the reaction affording a deteriorated mixture even if other factors are set appropriately. This situation probably means that the reaction centers, *i.e.*, two equivalent ester and/or intermediary formyl functionalities, must be *anti* to each other. Diagnosis of **4** by ^{13}C-NMR revealed unequivocally that **4** keeps axially dissymmetric C_2 chirality by indicating only eight-carbon signals, half of the real number of existing carbons.[3] Then, the two ester groups of **4** were reduced with DIBAL-H to diol (**5**)[4] and thus-generated hydroxyl groups were protected as benzyl ethers (**6**), in which, the acetonide group was splitted off as usual, giving rise to (4*R*,5*R*)-1,2-(bisbenzyloxy)-2(*E*),6(*E*)-octadien-4,5-diol (**7**) in 70% yield from **4** after silica gel chromatography.[5] Stereochemical analysis of **7** by ^1H- and ^{13}C-NMR spectroscopies has clarified again that an essential framework including chiralities and olefinic geometries has been absolutely preserved throughout the transformations.



a) 2,2-dimethoxypropane (1.1 eq)/p-TsOH/refl.; b) i. DIBAL-H (2.2eq)/PhCH3-hexane (1:1)/-78°C, 4 h. ii. $(i\text{-PrO})_2P(O)CH(Na)COOEt$ (5.0 eq)/THF/-78°C, 0.5 h and -78°C-0°C, 2 h; c) DIBAL-H(2.2 eq)/THF/-78°C, 3 h and -78°C-0°C, 2 h; d) BnBr(2.2 eq)/NaH(2.2 eq)/DMF/rt, 3 h; e) 2N-HCl(1.5 eq)/MeOH/80°C, 6 h.

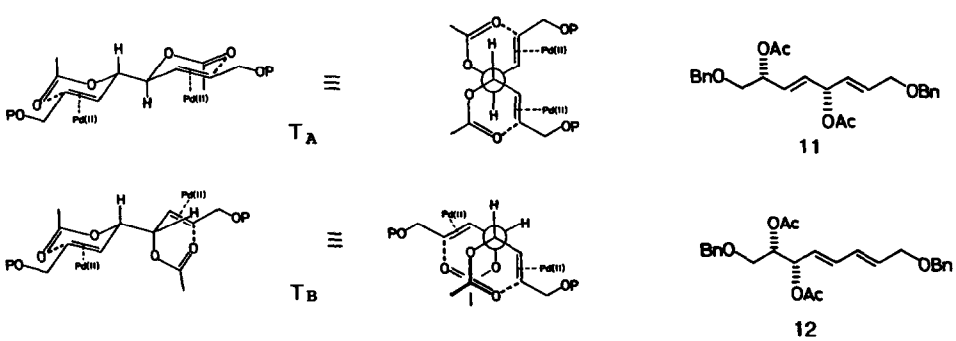
As quickly recognized from the structural feature of **7**, two set of [3,3]sigmatropic rearrangement system is seemingly able to be introduced by simply functionalizing the two hydroxyl groups located at C(4) and C(5). It turned out, however, that the Claisen rearrangement and available related variations were extremely a formidable challenge, none of these taking place in the desired way under the standard conditions.[6] To our delight, however, we have been rewarded by the method

for equilibrating allylic esters which uses the palladium(II) chloride complex of acetonitrile.[2] Thus, **7** was acetylated as usual to 4,5-(bisacetoxy)-2,6-diene (**8**), which, on exposure to $PdCl_2(CH_3CN)_2$ catalyst (10 mol% in THF at room temperature for 4 hours), gave (2*S*,7*S*)-1,8-(bisbenzyloxy)-2,7-(bisacetoxy)-3(*E*),5(*E*)-octadiene (**9**) in 82% yield after silica gel chromatography: $[\alpha]_D^{27}$ -41.0° (c 1.35, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.07 (s, 6H), 3.52 (dd, 2H, J_{gem}=10.6 Hz, J_{vic}=4.5 Hz, C(1,8)H_2), 3.55 (dd, 2H, J_{gem}=10.6 Hz, J_{vic}=6.4Hz, C(1,8)H_2), 4.52 (d, 2H, J_{gem}=12.2 Hz, BnOCH), 4.55 (d, 2H, J_{gem}=12.2 Hz, BnOCH), 5.48 (m, 2H, AcOCH), 5.68 (m, 2H, =CH-C(OAc)), 6.24 (m, 2H, =CH-C=), 7.30 (m, 10H); ^{13}C-NMR ($CDCl_3$, 126 MHz) δ 21.19(q), 71.19(t), 72.60(d), 73.20(t), 127.6(d), 127.7(d), 128.4(d), 129.4(d), 132.4(d), 137.8(s), 170.2(s): additionally, a COSY experiment for **9** has strongly supported that carbon-chain arrangement through C(1) to C(8) should be strictly that appeared as **9**. Moreover, in order to establish unequivocally the absolute stereochemistry around C(2) and C(7), **9** was transformed into glycerol acetonide derivative (**10**) through reasonable pathways, as shown below. The $[\alpha]_D$ value of **10** was essentially the same in magnitude with opposite sign as that of an authentic antipode derived from diethyl L-tartrate,[7] which led to the confirmation that the absolute configuration of **9** is (2*S*,7*S*).



$[\alpha]_D^{23}$ +20.2° (c 2.56, $CHCl_3$)

a) Ac_2 (2.4 eq)/DMAP (2.6 eq)/CH_2Cl_2/rt, 3hr; b) $PdCl_2(CH_3CN)_2$ (10 mol%)/THF/rt, 4 hr; c) O_3/MeOH/-78°C, then $(CH_3)_2S$; d) $NaBH_4$/MeOH; e) $LiAlH_4$/THF/-50°C; f) dimethoxypropane/acetone/H^+



Another possible conjugated diene-diol structure such as 2,3-(bisacetoxy)-4,6-diene framework (**12**) was not detected at all which is to be formed through a stepwise mechanism involving an intermediary

2,5-(bisacetoxy)-3,6-diene system (**11**).[8] Consequently, the palladium(II)-catalyzed [3,3]sigmatropic rearrangement of **8** has proceeded in highly concerted manner, both allylic-acetate moieties being involved simultaneously in the transition state which is indicated above as a double chair conformation still holding C_2 symmetry as a whole (**TA** or **TB**) and, thus, should be responsible for the complete translation of the original C-O chiralities at C(4) and C(5) to the migration termini with clean suprafacial stereochemistry. A reasonable final choice between them is open for further investigation because **TA** seems to be more probable than **TB** in terms of non-bonded interactions, whereas, in **TB**, the two σ-(C-C) bonds destined to constitute the conjugated π-bonds, are *anti*-periplanar relationship to each other which must play a role in lowering the energy of the corresponding transition state. The apparent irreversibility of the present rearrangement should be a consequence of the formation of stabilizing conjugated diene functionality.

Asymmetric Diels-Alder reactions utilizing thus-obtained diene and synthetic applications of chiral-building blocks with C_8 backbone presented in this work are currently our major concern, details of which will be reported in due course.

Acknowledgments: We are grateful to The SC-NMR Laboratory of Okayama University for ^1H (500 MHz)- and ^{13}C (126 MHz)-NMR experiments.

References and Notes

1) L. A. Paquette in "*Asymmetric Synthesis*", J. D. Morrison, Ed., Academic Press, New York, 1984, Vol. 3, pp 455-501.

2) a) P. M. Henry, *J. Am. Chem. Soc.*, 94, 5200 (1972); b) L. E. Overmann, *Angew Chem. Int. Ed. Engl.*, 23, 579 (1984) and references cited therein; for the first report which addressed the question of chirality transfer by means of this strategy, see P. A. Grieco, T. Takigawa, S. L. Bongers, and H. Tanaka, *J. Am. Chem. Soc.*, 80, 102 (1980).

3) **4**: ^{13}C-NMR ($CDCl_3$, 25 MHz) δ 14.23(q), 26.85(q), 60.63(t), 79.88(d), 110.8(s), 123.8(d), 142.0(d), 165.6(s); ^1H-NMR ($CDCl_3$, 100 MHz) δ 1.30 (t, 6H), 1.48 (s, 6H), 4.20 (q, 4H), 4.25 (m, 2H), 6.12 (dd, 2H, *J*=16 Hz, 1.5 Hz), 6.82 (m, 2H).

4) **5**: $[\alpha]_D^{27}$ +17.2° (c 1.0, CHCl3); ^1H-NMR ($CDCl_3$, 60 MHz) δ 1.45 (s, 6H), 2.30 (d, 2H), 4.05-4.30 (m, 6H), 5.70-6.25 (m, 4H).

5) **7**: $[\alpha]_D^{27}$ -20.5° (c 2.0, $CHCl_3$); ^1H-NMR ($CDCl_3$, 500 MHz) δ 4.02 (m, 6H, CHC=CCH2), 4.50 (s, 4H, PhCH2), 5.77 (ddd, 2H, *J*=15.6, 4.3, 1.3 Hz, =CH-C(OH)), 5.91 (dt, 2H, *J*=15.6, 5.4 Hz, BnOC-CH=), 7.28-7.37 (m, 10H); ^{13}C-NMR ($CDCl_3$, 126 MHz) δ 69.89(t), 72.24(t), 74.86(d), 127.63(d), 127.71(d), 128.4(d), 129.6(d), 131.28(d), 138.0(s).

6) We have executed Claisen [CH_2=CH-O-Et/$Hg(OAc)_2/\Delta$], Johnson's ortho ester [$MeC(OEt)_3/H^+/\Delta$], and Ireland's silylketene acetal [bisacetylation/LiHMDS/Me_3SiCl] rearrangements for **7** to result in the decomposition of the substrate or in the formation of multi-component mixtures.

7) The antipode has been obtained through benzylation of (*R*)-1,2-*O*-isopropylideneglycerol which was synthesized as reported (A. H. A.-Hakim, A. H. Haines, and C. Morley, *Synthesis*, 1985, 207): $[\alpha]_D^{27}$ -21.2° (c 4.33, $CHCl_3$).

8) For the pertinent system, see A. C. Oehlschlarger, P. Mishra, and S. Dhami, *Can. J. Chem.*, 62, 791 (1983) and B. T. Golding, C. Pierpoint, and R. Aneja, *J. Chem. Soc. Chem. Commun.*, 1030 (1981).

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