Access to an Optically Pure Cyclosarkomycin by Conversion of the *Endo* Adduct of (*R*)-Allene 1,3-Dicarboxylate and Cyclopentadiene

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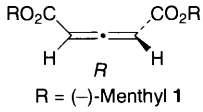
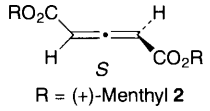
The enantioselective synthesis of (−)-cyclosarkomycin is accomplished using the *endo* 1:1 adduct of (*R*)-allene 1,3-dicarboxylate and cyclopentadiene.

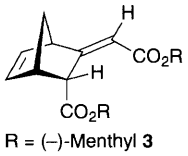
The asymmetric Diels–Alder reaction is extremely powerful since its remarkable regioselectivity, relatively predictable *endo* selectivity, *syn* stereospecificity and capacity to control the relative stereochemistry at up to four of the newly created chiral centres render this reaction unequalled in terms of elegance and efficiency in the construction of various chiral cyclohexene derivatives.[1] Recently we reported that the Diels–Alder reactions of optically active (*R*)- and (*S*)-allene 1,3-dicarboxylates **1** and **2** with cyclopentadiene in the presence of $AlCl_3$ as Lewis acid proceeded to afford the *endo* 1:1 adducts **3** and **4**, respectively, in high yields.[2] The results show that the Diels–Alder reaction proceeds with high π-diastereofacial selectivity derived from the approach of the diene to the less-hindered face of axial asymmetry of the allene moiety.

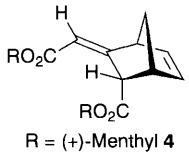
The *endo* adduct **3** is considered to be especially useful for the synthesis of optically active natural products. By way of example, we have attempted the synthesis of cyclosarkomycin **5**, a synthetic precursor of the antibiotic–antitumour sarkomycin **6**, which was produced by a strain of the soil microorganism *Streptomyces erythrochromogenes*;[3] only a limited number of enantioselective synthetic studies on the sarkomycin skeleton have been reported.[4,5]

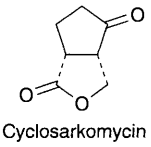
Stereospecific *cis*-bis-hydroxylation of the adduct **3** with a catalytic amount of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) in THF–Bu^{t}OH–H_2O gave the *exo* diol which was protected as its acetonide **7** (*p*-TsOH, anhydrous $CuSO_4$, acetone) in high yield (Scheme 1). Reduction of **7** with diisobutylaluminium hydride (DIBAH) gave the diol **8** (93%) together with recovery of (−)-menthol (96%). Ozonolysis (O_3, CH_2Cl_2, −78 °C) of **8** followed by quenching with dimethyl sulfide furnished the ketone **9**. Protection of the primary alcohol of **9** as the corresponding *tert*-butyldimethylsilyl (TBDMS) ether **10** followed by diastereoselective reduction with L-Selectride (THF, −78 °C) gave the secondary alcohol **11**. Attempts to protect the secondary alcohol of **11** by benzylation under a variety of conditions gave poor results. We then tried to protect the secondary alcohol of **11** *via* reductive cleavage of benzylidene acetals. Removal of the silyl group of **11** followed by protection of the diol **12** {benzaldehyde dimethylacetal, pyridinium toluene-*p*-sulfonate (PPTS), toluene, reflux} furnished the benzylidene acetals as a separable mixture (6:1) of diastereoisomers in 94% total yields. The hydrogenolysis of the mixture of benzylidene acetals using DIBAH gave the monobenzyl ether **13** in 72% yield. Removal of the isopropylidene protecting group of **13** by acid treatment (2 mol dm^{-3} HCl, DME, 80 °C) followed by periodate oxidation and subsequent Jones oxidation afforded the lactone **15**. Decarboxylation of **15** according to Barton's method[4] gave the lactone **16** {$[\alpha]_D^{23}$ −72.3 (*c* 1.11, $CHCl_3$)} in 67% yield, whose physical and spectral properties† were identical in all respects with those of Taguchi *et al.*,[5] while the optical purity of **16** still remains unknown due to the unavailability of the optical rotation.[6] Now, the formal synthesis of sarkomycin **6** can be accomplished since the conversion routes of **16** → **5**‡ → **6** have been reported by Taguchi *et al.*[5] and Marx *et al.*[3]

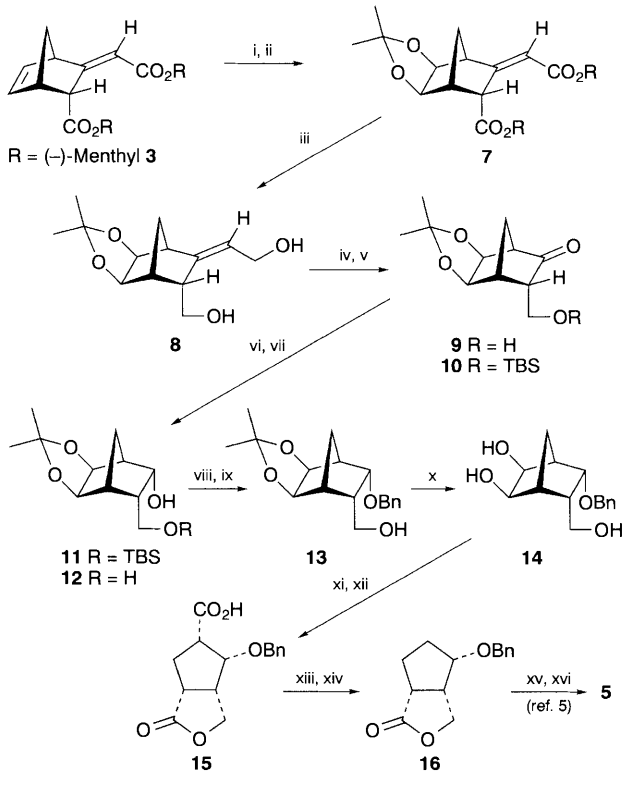












Scheme 1 *Reagents and conditions*: i, OsO_4(cat.), NMO, 95%; ii, *p*-TsOH, anhydrous $CuSO_4$, acetone, 98%; iii, DIBAH, CH_2Cl_2, −78 to 0 °C, 93%; iv, O_3, CH_2Cl_2, −78 °C, then Me_2S, CH_2Cl_2, −78 °C, 70%; v, TBDMSCl, imidazole, DMAP(cat.), CH_2Cl_2, 92%; vi, L-Selectride, THF, −78 °C, 84%; vii, 1% HCl, EtOH, 90%; viii, benzaldehyde dimethylacetal, PPTS, toluene, reflux, 94%; ix, DIBAH, toluene, −78 °C to room temp., 72%; x, 2 mol dm^{-3} HCl, DME, 80 °C, 71%; xi, $NaIO_4$; xii, Jones reagent (CrO_3, H_2SO_4, acetone), 89%, 2 steps; xiii, isobutyl chloroformate, *N*-methylmorpholine, THF, −15 °C, then 2-mercaptopyridine *N*-oxide, Et_3N, THF; xiv, Bu^{t}SH, irradition (300 W tungsten lamp), THF, 67%, 3 steps; xv, H_2, 20% $Pd(OH)_2$-C; xvi, Swern oxidation {$(COCl)_2$, Me_2SO, CH_2Cl_2, then Et_3N}

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Footnotes

† *Spectral data* for **16**: R_f 0.29 (ethyl acetate–hexane, 1 : 1); bp 147 °C/0.3 mmHg; IR ν/cm^{-1} (neat) 1760s; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.58 (dm, *J* 11.9 Hz, 2H), 4.42 (d, *J* 11.9 Hz, 1H), 4.23 (ddm, *J* 9.6, 8.3 Hz, 1H), 4.07–3.96 (m, 1H), 3.09–2.95 (m, 2H), 2.16–2.02 (m, 1H), 2.01–1.84 (m, 2H), 1.78–1.61 (m, 1H); LRMS (FAB) *m/z* (rel. inten.) 233 ($[M + H]^+$, 88); HRMS (FAB) *m/z* $[M + H]^+$ 233.1180 (calcd. for $C_{14}H_{17}O_3$, 233.1178).

‡ *Spectral data* for **5**: R_f 0.25 (ethyl acetate–hexane, 2 : 1); mp 60–61 °C; $[\alpha]_D^{23}$ − 415.0 (*c* 0.92, CH_2Cl_2) {lit.[4] mp 59.5–60 °C; $[\alpha]_D^{20}$ −397 (*c* 2.00, CH_2Cl_2)}; IR ν/cm^{-1} ($CHCl_3$) 1775s, 1745s; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.47 (dd, *J* 9.6, 2.6 Hz, 2H), 4.42 (dd, *J* 9.6, 7.3 Hz, 1H), 3.46–3.33 (m, 1H), 3.09–2.83 (m, 1H), 2.60–2.13 (m, 4H); LRMS (EI) *m/z* 140 (M^+).

References

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5 O. Kitagawa, T. Inoue and T. Taguchi, *Tetrahedron Lett.*, 1994, **35**, 1059.

6 T. Taguchi, personal communication: the specific rotation of **16**: $[\alpha]_D^{26}$ −66.7 (*c* 1.03, $CHCl_3$).