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DIMETHYL ($\underline{R}$)$_S$-2-(10-ISOBORNYLSULFINYL)MALEATE, A CHIRAL SYNTHETIC EQUIVALENT OF DIMETHYL ACETYLENEDICARBOXYLATE: PREPARATION AND ITS APPLICATION TO THE FORMAL CHIRAL SYNTHESIS OF (-)-NEPLANOCIN A AND (-)-ARISTEROMYCIN

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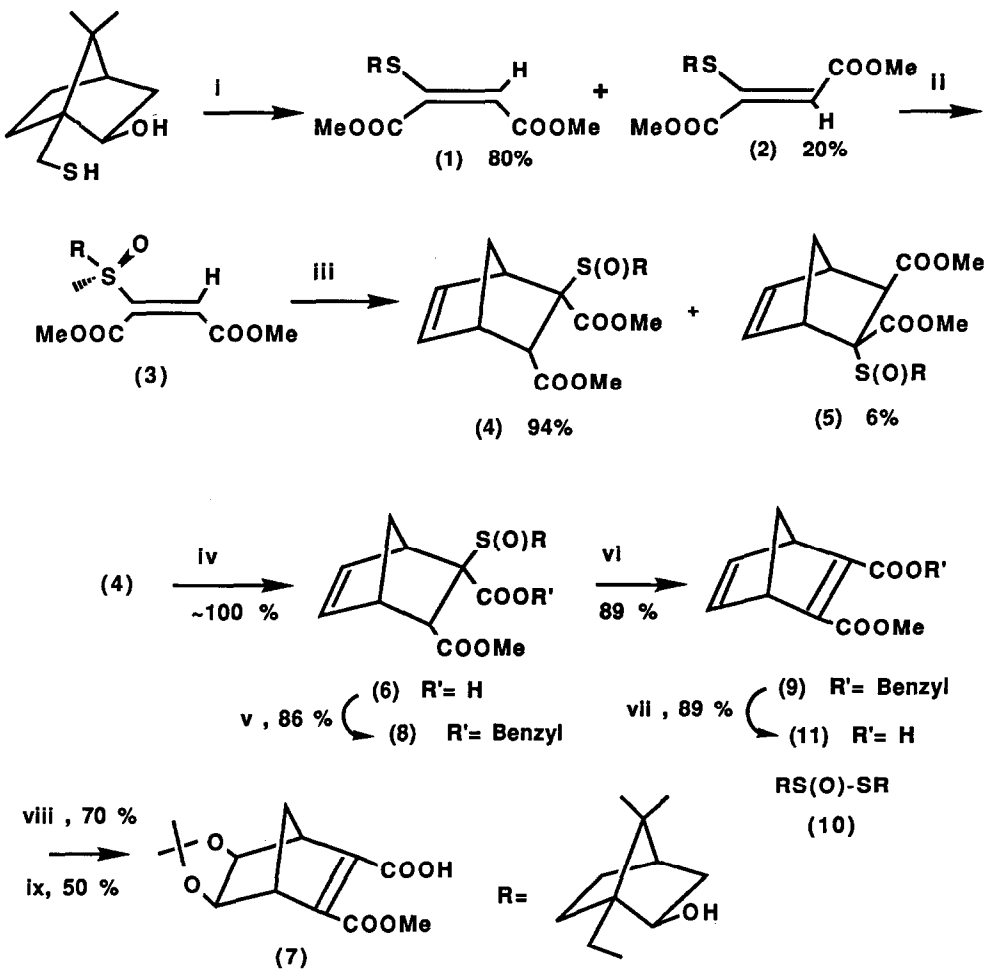
Summary--A novel chiral synthetic equivalent of dimethyl acetylenedicarboxylate, dimethyl ($\underline{R}$)$_S$-2-(10-isobornylsulfinyl)maleate (**3**), was synthesized. Diels-Alder reaction of (**3**) with cyclopentadiene proceeded with high stereo- and diastereo-selectivity to afford the cycloadduct (**4**) almost exclusively, which has been transformed into the half-ester (**7**), an intermediate in the synthesis of (-)-aristeromycin and (-)-neplanocin A.

Dimethyl acetylenedicarboxylate is one of the most versatile reagents[1] for the cycloaddition reactions and have been effectively utilized for the preparation of various kinds of natural products such as antibiotics and prostaglandin analogues[2]. If one can design its synthetic equivalent in an optically active form, the particular compound should be extremely valuable for the preparation of various biologically active compounds in optically pure forms. Dimethyl maleate having chiral sulfinyl substituent at 2 position seems to be a quite promising candidate for the purpose because the compound is expected to have satisfactory reactivity[3] and furthermore to give the corresponding cycloadducts in high diastereoselectivity as exemplified by the asymmetric Diels-Alder reaction using chiral sulfinyl ethenes[4]. In order to obtain this type of the compounds in optically pure form and to utilize for the asymmetric synthesis after the cycloaddition, the following synthetic problems should be overcome: a) the stereoselective formation of the 2-sulfenyl maleate over the corresponding fumarate. b) enantioselective or diastereoselective oxidation to chiral 2-sulfinyl derivative. c) selective demethylation of one of the two methoxycarbonyl groups in the cycloadduct prior to the desulfinylation step in order to avoid symmetrization $\underline{viz}$ racemization.

We noticed 10-mercaptoisoborneol as an auxiliary for the chiral sulfinyl group because we could expect the diastereoselective oxidation of the corresponding sulfenyl group[5] in the sulfenyl-maleate and the site-selective demethylation of the cycloadduct due to the directing effect of the secondary hydroxyl group. In this letter we describe our effort along this line on the preparation of the title compound and its successful application to the highly efficient formal synthesis of carbocyclic nucleosides, neplanocin A and aristeromycin[6].

Of several methods investigated, the following sequence was most effective (Scheme 1). Addition of 10-mercaptoisoborneol to dimethyl acetylenedicarboxylate in the presence of diphenylmethylphosphine[7] gave a 4:1 mixture of (**1**) and (**2**) quantitatively. Oxidation of this mixture with m-chloroperbenzoic acid (MCPBA), quite fortunately, produced the maleate-type sulfoxide (**3**), almost exclusively in 70% overall yield[8].



Scheme 1. Reagents and Conditions: i, DMAD, $MePh_2P$, MeCN, room temp., 12 hr; ii, m-chloroperbenzoic acid, CH_2Cl_2, 0 °C, 3 h; iii, C_5H_6, $ZnCl_2$, CH_2Cl_2, -20 °C, 2.5 h; iv, $AlBr_3$, Me_2S, CH_2Cl_2, 0 °C, 4 h; v, $C_6H_5CH_2Br$, NaH, 18-crown-6, MeCN, 50 °C, 12 h; vi, 1,8-diazabicyclo[5.4.0]undec-7-ene, PhH, 50 °C, 12 h; vii, $AlCl_3$, $MeNO_2$, Me_2S, CH_2Cl_2, room temp., 48 h; viii, OsO_4, Me_3NO, t-BuOH, 0 °C, 3 h; $Me_2C(OMe)_2$, p-TsOH, acetone, 70 °C, 7 h; ix, 5 % Pd-C, MeOH, cyclohexa-1,3-diene, 40 °C, 40 h.

Although the reasons for the selectivity and the isomerization are not obvious, the highly diastereoselective oxidation with MCPBA might reflect the directing effect of the secondary hydroxyl group in the chiral auxiliary. The absolute stereochemistry of (**3**) could not be determined at this stage: however, the absolute configuration and the olefinic geometry were finally determined by a single crystal X-ray analysis of the major cycloadduct (vide infra).

Having the chiral dienophile (**3**) in hand, we examined the cycloaddition with cyclopentadiene. After several attempts to optimize the diastereoselectivity and the yields, the reaction conducted at -20 °C in the presence of zinc chloride turned out to be most diastereoselective to provide exclusively the single exo-sulfoxide (**4**)(92%), along with a small amount of the endo-isomer (**5**)(6%)[9]. A single crystal X-ray analysis of (**4**) revealed that the absolute stereochemistry of the sulfur center had R configuration[10]. After the several attempts, selective demethylation of (**4**) was successfully achieved using dimethyl sulfide-aluminium bromide[11] to afford quantitatively the half-ester (**6**), whose structure could be determined by further transformation into the ester (**7**) with known absolute configuration[12]. Although attempts to convert (**6**) directly into (**7**) by base treatment or by heating were unsuccessful, the benzyl ester (**8**) which was easily derived from (**6**) gave the diene ester (**9**) in 90% yield[13] on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene. Deprotection[14] of (**9**) afforded the half-ester (**11**) in optically pure form[15].

cis-Hydroxylation of (**9**) and subsequent acetonidation followed by debenzylation gave the half-ester (**7**) (m.p. 117-117.5 °C, $[\alpha]_D^{25}$ -29.5° (c 1.2, $CHCl_3$)) in 56% yield. The enantiomeric excess (e.e.) of (**7**) was proved to be no less than 92 % by NMR measurement of the corresponding (L)-α-phenylethylamide[16] and comparison of the specific rotation with the reported value (lit.[6a] $[\alpha]_D^{25}$ -23.8° (c 1.17, $CHCl_3$), e.e. 80%).

From the above results, it is noteworthy that the Diels-Alder reaction of (**3**) proceeded in a highly diastereoselective manner and the structure of (**7**) obtained by selective demethylation was established to be as depicted in Scheme 1. The half-ester (**7**) has been employed as a chiral starting material in the synthesis of carbocyclic nucleosides, (-)-aristeromycin and (-)-neplanocin A. The cycloaddition using the sulfoxide (**3**) would provide a new route to the chiral synthesis of carbocyclic nucleosides and other natural products such as prostaglandins. Further investigation of asymmetric cycloaddition using this novel chiral dienophile with other dienes such as butadiene is now in progress in this laboratory.

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8)All new compounds gave satisfactory analytical (combustion and/or high resolution mass spectrum) and spectral data.
MCPBA oxidation of the compounds **1** and **2** afforded the sulfoxide **3** in 91% and 50 % yields, respectively. Compound (**3**): $[\alpha]_D^{25}$ +32.8°(c 3.1, $CHCl_3$), ^1H n.m.r. ($CDCl_3$, 270 MHz) δ 0.84 (s, 3 H, Me), 1.07 (s, 3 H, Me), 1.1-1.8 (m, 7 H), 2.90 (d, 1 H, J 13 Hz, SCH), 3.05 (d, 1 H, J 13 Hz, SCH), 3.86 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.10 (m, 1 H, OCH), 6.98 (s, 1 H, CH=), IR ν_{max} ($CHCl_3$) 3470 (OH), 1730 (C=O) cm^{-1}.
9) The cycloaddition of **3** and cyclopentadiene without Lewis acid catalyst(room temp., 12hr) afforded the adducts in the following ratios: exo sulfoxides (68% , **4**:another diastereomer=7:93); endo sulfoxides(12 % , **5**:another diastereomer=0:100). The similar chelation controlled D-A reaction has been reported. see ref. 4b.
10) Crystal data: M=410.5, monoclinic, space group $P2_1$, a=21.650(7). b=7.027(2), c=6.918(3) A, β=98.74(3) , V=1040.2(6) $Å^3$, D_c=1.311 g cm^{-3}, Z=2, (Cu-Kα)=1.54178 Å, crystal size 0.3x0.1x0.1 mm. Data were collected with Cu-Kα radiation on a Rigaku AFC-5 diffractometer system. A total of 1559 unique reflections were measured; 1298 with $|F_0|>3\sigma(F_0)$ were used for structure solution by direct method (MULTAN84). The final residuals were R=0.088 and R_w=0.120,large R value being probably due to poor quality of the crystal used. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.
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