A FACILE SYNTHESIS OF 4-ARYL-5-HYDROXY-(2*E*)-PENTENOATE DERIVATIVES AND ITS APPLICATIONS TO THE FIRST SYNTHESIS OF (±)-CURUCUDIOL, (±)-CURCUHYDROQUINONE AND (±)-CURCUQUINONE

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Abstract----The first syntheses of three kinds of bisabolane sesquiterpenes, (±)-curcudiol (**29**), (±)-curcuhydroquinone (**40**) and (±)-curcuquinone (**41**) were achieved based on the $BF_3 \cdot Et_2O$ catalyzed reaction of (±) methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) and polymethoxytoluene.

The bisabolane family are a group of sesquiterpenes having the simplest monocarbocyclic skeleton. Although the numerous syntheses of racemic form have been reported,[1] none have been synthesized in optically active form. For the purpose of chiral synthesis, the existence of the hydroxylmethyl group at the benzylic position of the bisabolane congener should be required at least because optical resolution should be possible based on a clue of the existing primary hydroxylmethyl group and the hydroxylmethyl group can be converted into methyl group. This communication describes a new and very direct route to bisabolane sesquiterpenes, as illustrated by the preparation of (±) methyl 4-aryl-5-hydroxy-(2*E*)-pentenoate derivatives (**A** or **B**), being synthetic intermediate for the syntheses of them. In order to achieve the above aim, a new and simple reaction to get the pentenoate derivatives (**A** and **B**) should be developed. The reactions of α,β-epoxyester and nucleophiles such as alcohols and phenols in the presence of Lewis acid are reported to give α,β-disubstituted esters (β-adducts),[2a] while γ-position of γ,δ-epoxyacrylate having a vinylogous structure of α,β-epoxyester have been reported to be attacked

by nucleophiles such as organometallic compounds. [2b,c]   According to the above mentioned observations, the desired products should be obtained by the Lewis acid catalyzed reaction of (±) methyl 4,5-epoxy-(2E)-pentenoate (1) and various kinds of aromatic nucleophiles.   The reaction of (±)-1 and various kinds of polymethoxybenzenes or polymethoxytoluenes in the presence of $BF_3 \cdot Et_2O$ proceeded at -78°C to give 4-substituted products (A or B),[3] as main products along with 2-substituted products (C or D)[3] as shown in table. The typical structure determination using (±)-7[4] and (±)-8[4] was carried out by nmr analysis and chemical correlation.   DIBAL-H reduction of (±)-7 and (±)-8 gave the same diol (20).   The substitution pattern in the aromatic ring of (±)-7 and (±)-8 was determined by a nuclear Overhauser effect (NOE) experiment as shown in chart.   The regioselectivity of the nucleophilic reagent toward (±)-1 was found to be subtly affected by reagents used.   In the reaction of (±)-1 with nucleophiles in the presence of $BF_3 \cdot Et_2O$, the possibility of forming the π-allyl comlex (21) (see table) from (±)-1 should be considered.   The detailed discussion will be mentioned in the forthcoming paper.

Then the first syntheses of (±)-curcudiol (29), (±)-curcuhydroquinone (40) and (±)-curcuquinone (41) formally derived from (±)-40, were achieved from (±)-6 and (±)-13, respectively.   Catalytic hydrogenation of (±)-6 gave (±)-22 (99%) followed by treatment of tosyl chloride to afford (±)-23 (91%). $NaBH_4$ reduction of (±)-23 provided (±)-24 (25%) and (±)-25 (57%).   Conversion of (±)-25 into the one-carbon homologation product ((±)-27) was achieved by the standard procedure (tosylation, (±)-26 (77%), CN-substitution, (±)-27 (93%)). An alkaline hydrolysis of (±)-27 followed by the successive demethylation and esterification gave the methyl ester ((±)-28) (overall yield 60% from (±)-27), which was treated with Grignard reagent to afford (±)-curcudiol (29) (70%).   The spectral data (ir, nmr and ms) of the synthesized (±)-29 were identical with those of natural (+)-curcudiol (29).[5]   The synthesis of (±)-curcuhydroquinone (40) from (±)-13 was carried out by the same way as that of (±)-29.   Conversion of (±)-13 into the alcohol ((±)-33) was achieved by the same route ((±)-31, 86% overall yield from (±)-13, (±)-32 (16%) and (±)-33 (73%) as the previous case ((±)-6 → (±)-25). Acetylation ((±)-34; 96%) of (±)-33 followed by demethylation provided the hydroquinone analog ((±)-35), which was treated with MOMCl to give the MOM ether ((±)-36) in 71% overall yield from (±)-34.   Hydrolysis ((±)-37, 88%) of (±)-36 followed by oxidation provided the aldehyde ((±)-38), which was subjected to the Wittig reaction to afford (±)-39 (26% overall yield from (±)-37).   Deprotection of (±)-39 gave (±)-curcuhydroquinone (40; 61%), which was oxidized with CAN to provide (±)-curcuquinone (41) in 23% yield.[7] The spectral data (ir, nmr and ms) of (±)-40 and (±)-41 were identical with those of natural products ((-)-40[6]
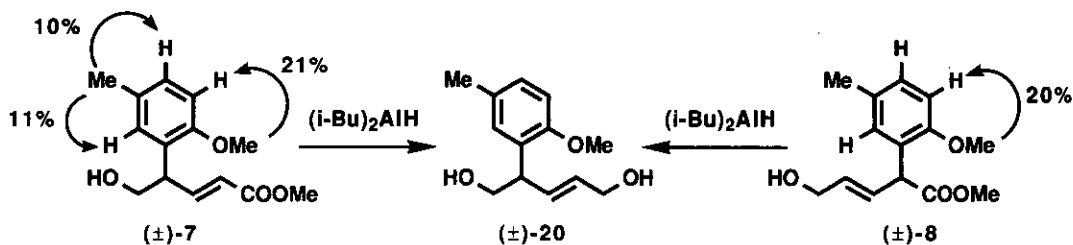
Table

bisabolane skeleton
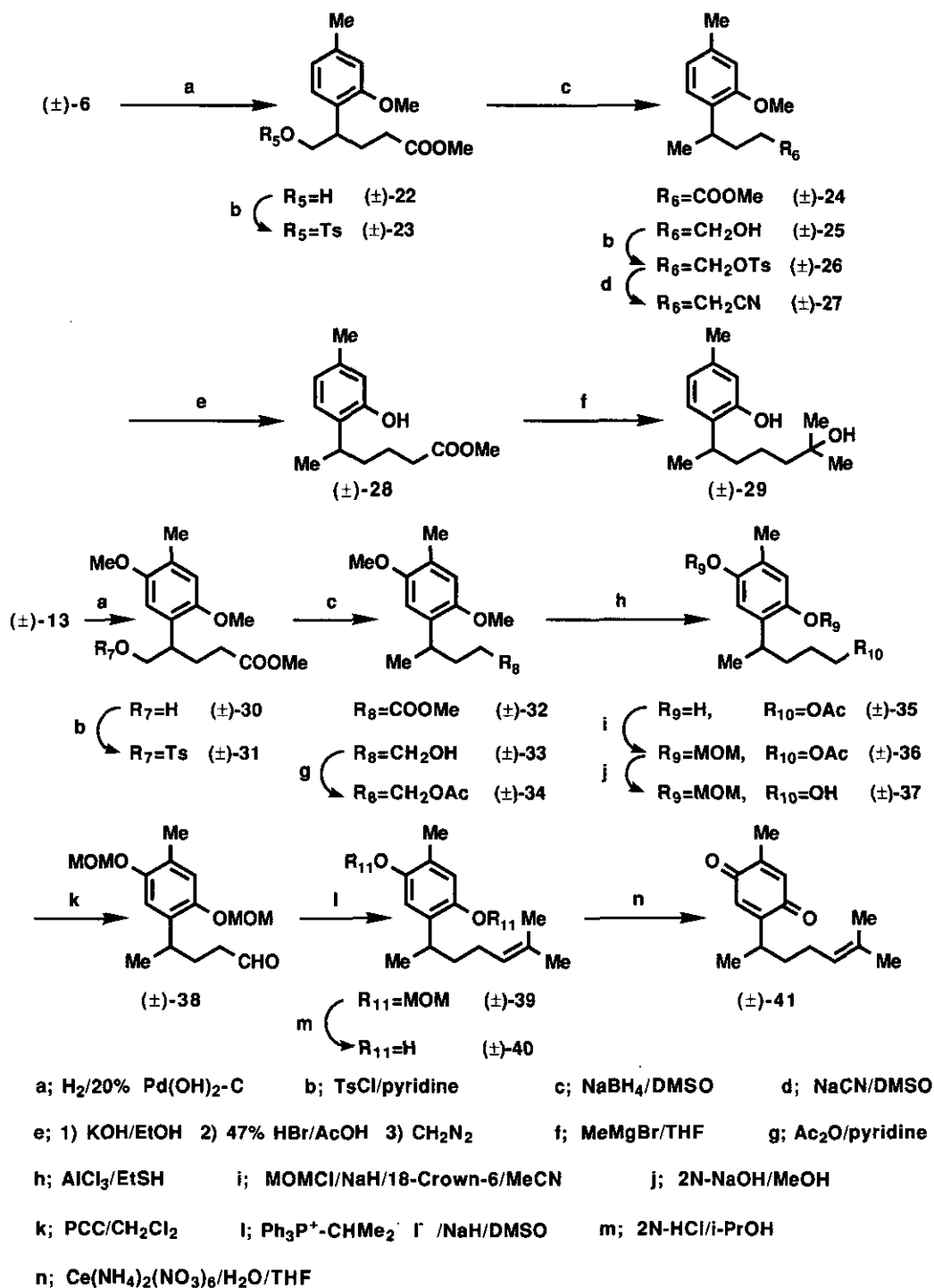
(±)-1
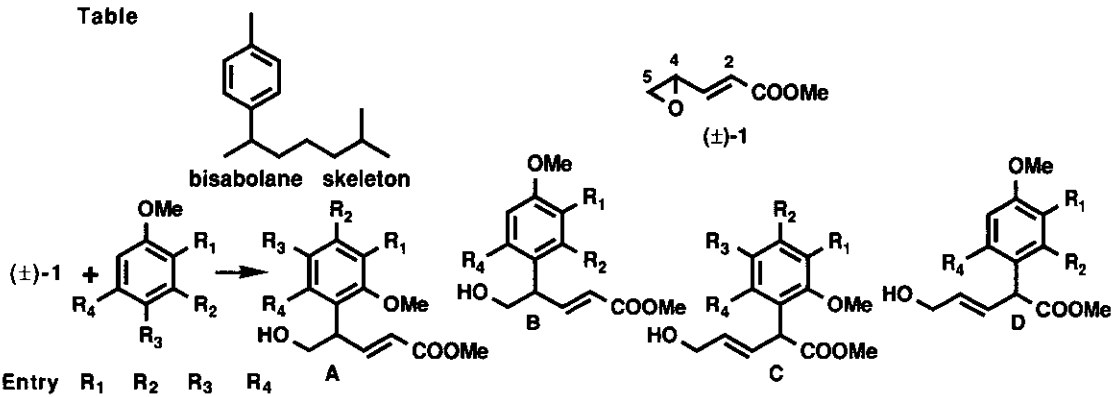
Entry	R_1	R_2	R_3	R_4	A	B	C	D
1	H	H	H	H	(±)-3 (10%)	(±)-2 (71%)		
2	Me	H	H	H		(±)-4 (86%)		
3	H	Me	H	H	(±)-6 (23%)	(±)-5 (49%)		
4	H	H	Me	H	(±)-7 (42%)		(±)-8 (18%)	
5	OMe	H	H	Me		(±)-9 (46%)		(±)-10 (18%)
6*	H	OMe	H	Me		(±)-11 (82%)		
7	H	Me	OMe	H	(±)-13 (68%)		(±)-14 (11%)	
8	OMe	H	H	H		(±)-15 (73%)		(±)-16 (5%)
9	H	OMe	H	H		(±)-17 (70%)		
10	H	H	OMe	H	(±)-18 (50%)		(±)-19 (6%)	

21
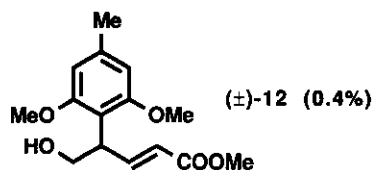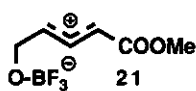
(±)-12 (0.4%)

*In Entry 6, the (±)-2,4,6-trisubstituted product (±)-12 (0.4%) was additionally obtained.

(±)-7   (i-Bu)$_2$AlH →   (±)-20   ← (i-Bu)$_2$AlH   (±)-8

a; H$_2$/20% Pd(OH)$_2$-C   b; TsCl/pyridine   c; NaBH$_4$/DMSO   d; NaCN/DMSO

e; 1) KOH/EtOH 2) 47% HBr/AcOH 3) CH$_2$N$_2$ f; MeMgBr/THF   g; Ac$_2$O/pyridine

h; AlCl$_3$/EtSH   i; MOMCl/NaH/18-Crown-6/MeCN   j; 2N-NaOH/MeOH

k; PCC/CH$_2$Cl$_2$ l; Ph$_3$P$^+$-CHMe$_2$ I$^-$ /NaH/DMSO   m; 2N-HCl/i-PrOH

n; Ce(NH$_4$)$_2$(NO$_3$)$_6$/H$_2$O/THF

Scheme

and (-)-**41**[6]), respectively.   In conclusion, we have carried out the first syntheses of (±)-**29**, (±)-**40** and (±)-**41** based on the reaction of (±) methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) and polymethoxytoluene in the presence of $BF_3.Et_2O$.   The optical resolutions of the primary alcohols ((±)-**6**, (±)-**22**, (±)-**13** and (±)-**30**) are in progress.

ACKNOWLEDGMENT

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3 Satisfactory analytical data were obtained for all new compounds.

4 Spectral data of (±)-**7** and (±)-**8**.   (±)-**7**: ir(CCl_4) 3430, 1700 cm^{-1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.88 (1H,br s, OH), 2.27 (3H, s, aromatic Me), 3.71 (3H, s, COOMe), 3.79 (3H, s, OMe), 3.89 (2H, d, J=7 Hz, C_5-H), 4.08 (1H, q, J=7 Hz, C_4-H), 5.91 (1H, d, J=16 Hz, C_2-H), 6.78 (1H, d, J=8 Hz, $C_{3'}$-H), 6.93 (1H, d, J=2 Hz, $C_{6'}$-H), 7.03 (1H, dd, J=8, 2 Hz, $C_{4'}$-H), 7.18 (1H, dd, J=16, 7 Hz, C_3-H); m/z (EI-ms) 250 (M$^+$): (±)-**8** ir (CCl_4) 3440, 1715 cm^{-1}; 1H-nmr (400 MHz, $CDCl_3$) δ 1.80 (1H, br s, OH), 2.27 (3H, s, aromatic Me), 3.67 (3H, s, COOMe), 3.78 (3H, s, OMe), 4.13 (2H, d, J=6 Hz, C_5-H), 4.58 (1H, d, J=8 Hz, C_2-H), 5.69 (1H, dt, J=16, 6 Hz, C_4-H), 6.05 (1H, dd, J=16, 8 Hz, C_3-H), 6.77 (1H, d, J=8 Hz, $C_{3'}$-H), 7.01 (1H, d, J=2 Hz, $C_{6'}$-H), 7.06 (1H, dd, J=8, 2 Hz, $C_{4'}$-H); m/z (EI-ms) 250 (M$^+$).

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7 Reaction conditions were not optimized.