A New Route to Substituted 3-Methoxycarbonyldihydropyrans; Enantioselective Synthesis of (−)-Methyl Elenolate

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A stereoselective chiral synthesis of (−)-methyl elenolate has been achieved by employing a newly developed method for the construction of substituted 3-methoxycarbonyldihydropyrans based on a radical cyclisation reaction.

A number of secoiridoid monoterpenes and biogenetically related heteroyohimbine indole alkaloids possess characteristic highly substituted 3-methoxycarbonyldihydropyran ring systems, as exemplified by elenolic acid (**1**), sarracenin (**3**), and ajmalicine (**4**). The stereoselective assembly of these ring systems is one of the most crucial problems in the synthesis of this family of compounds.[1,2] For the purpose of developing an effective method for the construction of substituted 3-methoxycarbonyldihydropyrans, we chose methyl elenolate (**2**)[3] as a synthetic target. Methyl elenolate (**2**) is the methyl ester of elenolic acid (**1**), a secoiridoid monoterpene isolated from olive (*Oleau europea*).[4] The combination of its broad-range antiviral activity[5] and its synthetic utility[3a] as a precursor of ajmalicine (**4**), a therapeutically important heteroyohimbine indole alkaloid, made (**2**) an attractive target. We now report an enantio- and stereo-selective synthesis of (−)-methyl elenolate (**2**) by use of a new methodology based on a radical cyclisation reaction.[6]

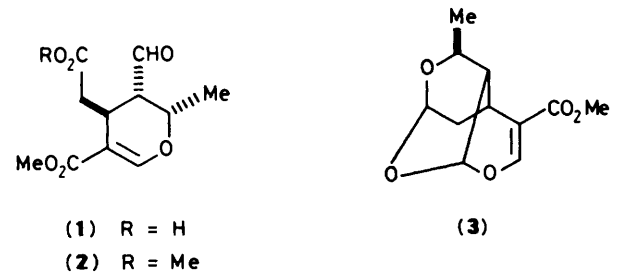
Initially, our strategy was tested in a model study as follows. Thus, five bromoacetals (**6a—e**)† were prepared from the corresponding δ-hydroxy α,β-unsaturated esters (**5a—e**) by addition[7] of methyl propiolate followed by treatment with *N*-bromosuccinimide (NBS) in methanol. Reaction[8] of (**6a—e**) with tributyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) in boiling benzene followed by treatment with acid in the same flask led to formation of the 3-methoxycarbonyldihydropyran derivatives (**7a—e**). The yield and the stereochemical outcome of this reaction sequence are summarized in Table 1.

Table 1. Synthesis of 3-methoxycarbonyldihydropyrans (**7a—e**).

(**5**)	% Yield of (**6**)	% Yield of (**7**) (*syn* : *anti*)[a]
a; $R^1 = H, R^2 = H$	86	80
b; $R^1 = Me, R^2 = H$	83	74 (3 : 1)
c; $R^1 = H, R^2 = Me$	89	74 (1 : 3)
d; $R^1 = Me, R^2 = Me$ (*anti*)	94	64 (1 : 2)[b]
e; $R^1 = Me, R^2 = Me$ (*syn*)	94	80 (1 : 3)[b]

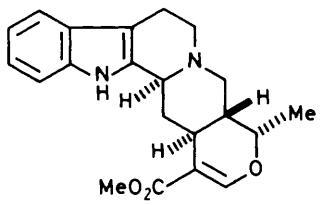
[a] Determined by 500 MHz ^1H n.m.r. [b] Relative configuration between C-4 and C-5.

† All new compounds exhibited satisfactory spectral (^1H n.m.r., i.r., and high resolution mass) data.



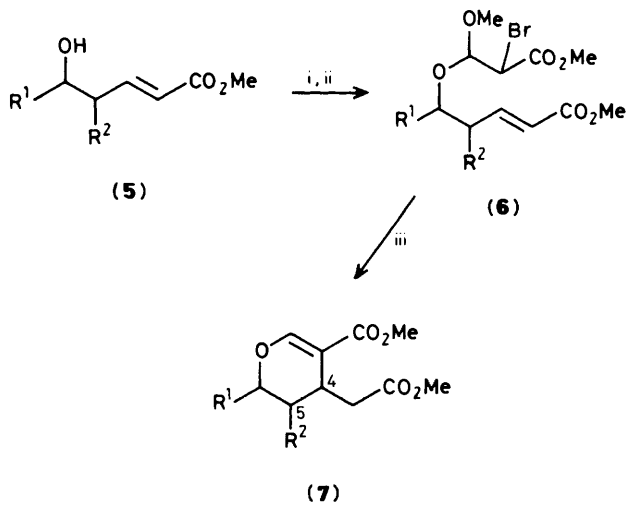
(1) R = H
(2) R = Me

(3)



(4)

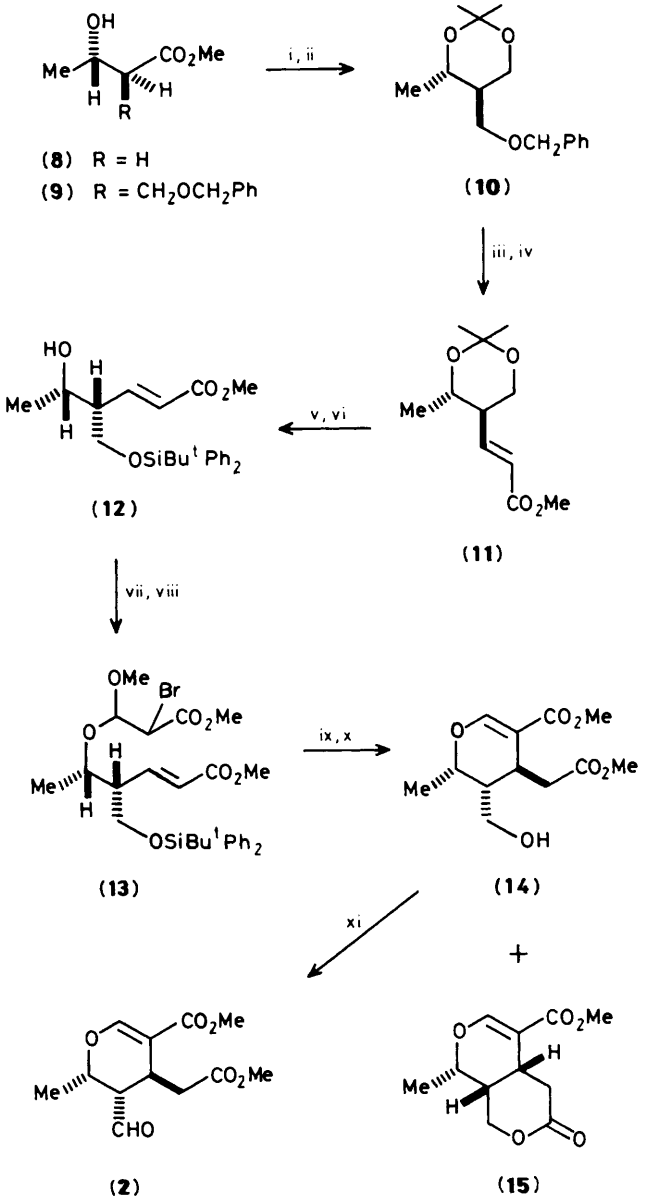
Scheme 1



(5) (6) (7)

Scheme 2. *Reagents and conditions*: i, methyl propiolate (3.5 equiv.), *N*-methylmorpholine (26 mol%), toluene; ii, NBS (1.2 equiv.), $NaHCO_3$ (1.3 equiv.), MeOH; iii, Bu^n_3SnH (1.2 equiv.), AIBN (5 mol%), benzene, reflux (1 h), then add TsOH (40 mol%), reflux (1 h).

Having established a new method for the construction of substituted 3-methoxycarbonyldihydropyrans, we investigated the synthesis of (**2**). The hydroxy ester (**9**),[9] prepared from commercially available (*S*)–methyl 3-hydroxybutyrate (**8**) (78% enantiomeric excess)‡ by stereoselective alkylation, was subjected successively to reduction and protection to give the acetonide (**10**), $[\alpha]^{25}$ −16.8° (*c* 1.01, $CHCl_3$),§ in 70% yield. Upon sequential debenzylation, Swern oxidation, and Wittig reaction,[10] the α,β-unsaturated ester (**11**), $[\alpha]_D^{19}$ −28.6° (*c* 1.01, $CHCl_3$), was obtained in 95% overall yield from (**10**). Acid hydrolysis followed by selective silylation afforded the *O*-silyl derivative (**12**),¶ $[\alpha]_D^{23}$ −9.0° (*c* 0.98, $CHCl_3$), in 92% yield. Compound (**12**) was converted into the



(8) R = H
(9) R = CH_2OCH_2Ph

(10) (11) (12) (13) (14) (2) (15)

Scheme 3. *Reagents and conditions*: i, $LiAlH_4$, THF; ii, $Me_2C(OMe)_2$, TsOH, acetone; iii, Li, liq. NH_3/THF, −33 °C; iv, $(COCl)_2$/Me_2SO/Et_3N, CH_2Cl_2, −50 to 25 °C, then add $Ph_3P{=}CHCO_2Me$; v, 1M HCl/THF (1 : 1); vi, Ph_2Bu^tSiCl, imidazole, CH_2Cl_2; vii, methyl propiolate (3.5 equiv.), *N*-methylmorpholine (26 mol%), toluene; viii, NBS (1.2 equiv.), $NaHCO_3$ (1.3 equiv.), MeOH; ix, Bu^n_3SnH (1.2 equiv.), AIBN (5 mol%), benzene, reflux (1 h), then add TsOH (40 mol%), reflux (1 h); x, 46% aq. HF/MeOH (1 : 3); xi, $(COCl)_2$/Me_2SO/Et_3N, CH_2Cl_2, −50 to 25 °C.

‡ The optical purity of (**8**), purchased from Wako Pure Chemical Industries Ltd., was determined on the basis of the specific rotation, α_D^{24} +18.4° (neat) [enantiomerically pure enantiomer:[11] α_D^{22} −23.5° (neat)]. This value was consistent with that determined by 500 MHz ^1H n.m.r. analysis of both *R*- and *S*-methoxy(trifluoromethyl)phenylacetyl ester derivatives of (**9**).

§ All the optical rotations reported here should be regarded as corresponding to 78% enantiomeric excess.

¶ The structure of (**12**) was confirmed by 90 MHz ^1H n.m.r. analysis of the corresponding acetate, δ ($CDCl_3$) 1.06 (9H, s), 1.16 (3H, d, *J* 6.8 Hz), 1.97 (3H, s), 2.62 (1H, m), 3.70 (2H, d, *J* 6.5 Hz), 3.77 (3H, s), 5.15 (1H, quint, *J* 6.8 Hz), 5.90 (1H, dd, *J* 15.5 and 1.1 Hz), 6.91 (1H, dd, *J* 15.5 and 8.5 Hz), 7.27—7.80 (10H, m).

bromo acetal (**13**) in 89% yield in a manner similar to that described for the model study. Upon radical cyclisation followed by acid treatment in the same flask and desilylation, (**13**) yielded the alcohol (**14**), $[\alpha]_D^{24}$ −62° (*c* 0.89, $CHCl_3$), and the lactone (**15**) in the ratio 4 : 1, in 58% yield. Finally, Swern oxidation of (**14**) furnished (−)-methyl elenolate (**2**) in 88% yield. The synthetic substance exhibited spectral properties (500 MHz ^1H n.m.r., i.r., and mass) in accord with those of an authentic sample.[3b] The optical rotation, $[\alpha]_D^{23}$ −94.7° (*c* 0.76, $CHCl_3$) [lit.,[3c] −121° (*c* 0.68, $CHCl_3$)], shows that there is no racemisation step in the present synthetic route, since the optical purity of (**2**) was almost identical with that of the starting ester (**8**). Purification of (**2**) (h.p.l.c. on octadecylsilane) allowed us to obtain a pure sample without any epimerisation at the position α to the formyl group.‖

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‖ Column chromatography (SiO_2; 1 : 1 ether–hexane) brought about epimerisation, to give a 88 : 12 mixture of (**2**) and its epimer, respectively.