Pergamon

Tetrahedron Letters, Vol. 35, No. 43, pp. 7949-7952, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01722-0

An Efficient Route to the Formal Total Synthesis of A-seco Mevinic Acid Analogues

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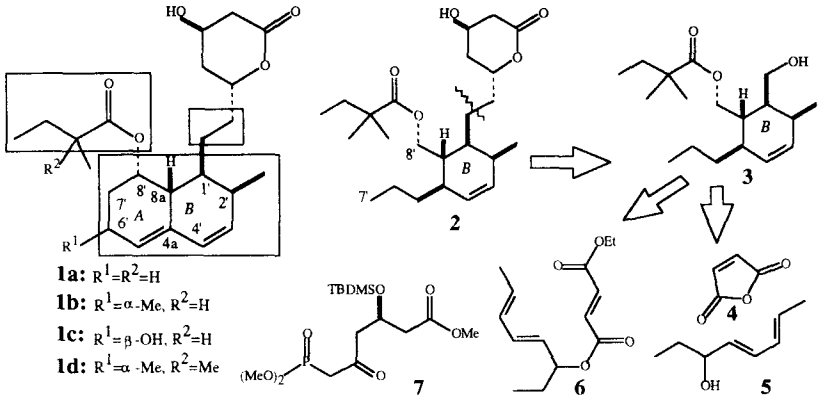
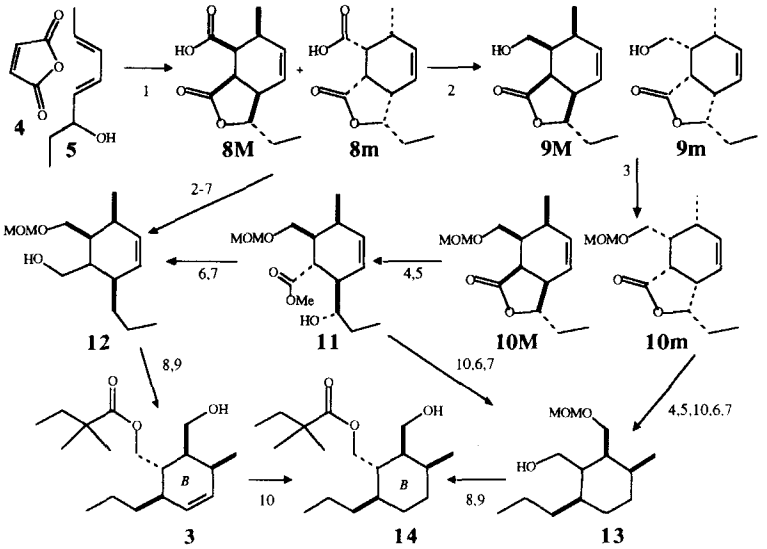
Abstract: *A short, stereocontrolled access to the fully functionalized B-ring together with a chemobiological approach to the 1,2,3,4-tetrasubstituted cyclohexene unit of A-seco mevinic acids is presented.*

Subsequent to the first reports disclosing the structure and biological activity of compactin[1] **1a** and mevinolin[2] **1b**, extensive studies directed toward their total synthesis and the development of structurally simplified HMG-CoA reductase inhibitors containing the prerequisite 3,5-dihydroxyheptanoic acid side chain and a hydrophobic moeity able to mimic the hexalin portion of the naturally occuring inhibitors have appeared. [3] One of the possible modifications[4] consists on the synthesis of A-seco mevinic acids, with a C7'-C8' bond cleavage leading to a monocyclic analogue.[5] Two syntheses have been reported recently for the fully functional A-seco analogues. In the first synthesis, a monocyclic analogue of compactin was prepared by a multistep transformation of pravastatin **1c**.[6] More recently a second approach was reported starting from levoglucosan.[7] Herein we describe a simple procedure for the synthesis of our target molecule **3**, an A-seco mevinic acid precursor. The four contiguous stereogenic centers are installed using an inter and intramolecular Diels-Alder strategy.



The Intermolecular Diels-Alder route: Diene **5** is readily obtained by reacting sorbic aldehyde with an excess of ethyl lithium in ether at -78°C (>95% yield) and allowed to react with maleic anhydride **4** (48mmol of **5**, 72 mmol of **4** in 200 ml of dry benzene, 24 h reflux under argon) thus affording, after spontaneous lactonization,[8] adducts **8M** and **8m** in a 2:1 ratio and 83% yield. The crude mixture of lactone acids is then transformed into alcohols **9M** and **9m** by chemoselective reduction of the carboxyl group[9](oxalyl chloride, then

excess $NaBH_4$, in DMF-THF at -78°C, 85% yield). The resulting alcohols **9M** and **9m** are easily separated by silica gel flash chromatography (ethyl acetate-heptane, 1:1). Either the pure lactone alcohols **9M** and **9m** or the mixture **9M+9m** (since the final compound is devoid of the stereogenic center at C-5') were converted to the target compound **3**. Among the different protections of the primary alcohol (TBDMS, TBDPS, BOM) the MOM group was the best choice for the remaining transformations. Thus 2.38 mmol of **9** in 8 ml of dichloromethane were treated with 6 mmol of $i Pr_2NEt$ followed by addition of 5.26 mmol of MOMCl to give **10** in a quantitative yield. Lactone opening and epimerization at C-8a was carried out by simply heating 2.16 mmol of the MOM-protected alcohols in 15 ml of 7.5 N aq NaOH at 100°C, for 12h . Acidification with conc. HCl, extraction with ethyl acetate, solvent removal, followed by esterification with diazomethane (Et_2O, 0°C, 100%, two steps) set the stage for the tetrasubstituted cyclohexene derivative **11** with the desired configurations at C-1', C-2', C-8a and C-4a (trans-dihydrocompactin/mevinolin monocyclic analogue) in five steps. Mesylation (3.5 mmol of **11** in 20 ml of CH_2Cl_2, 8.6 mmol of Et_3N and 6.5 mmol of MsCl , r.t., 10 min, 98%) followed by Li-NH_3 reduction (1.26 mmol of the mesylate in 100 ml of liquid ammonia, 20 eq. of lithium metal at -78°C, followed by addition after 10 min of 7 eq. of ethanol, 86%) insured both deoxygenation at C5' and reduction of the ester functionality leading to the monoprotected diol **12**, ready to be re-esterified as required. Thus, **12** (0.78 mmol) was esterified with 2,2-dimethylbutyryl chloride [10](1.09 mmol) in CH_2Cl_2 (10 ml), in the presence of Et_3N (2.34 mmol) and DMAP (0.4 mmol), at r.t. for 20 min (90%). Subsequent deprotection using $BF_3.Et_2O$ (2.44 mmol, 4.4 eq.) and ethanedithiol (0.12 mmol, 4.4 eq.) in CH_2Cl_2 (20 ml) afforded quantitatively the target **3** .[11]

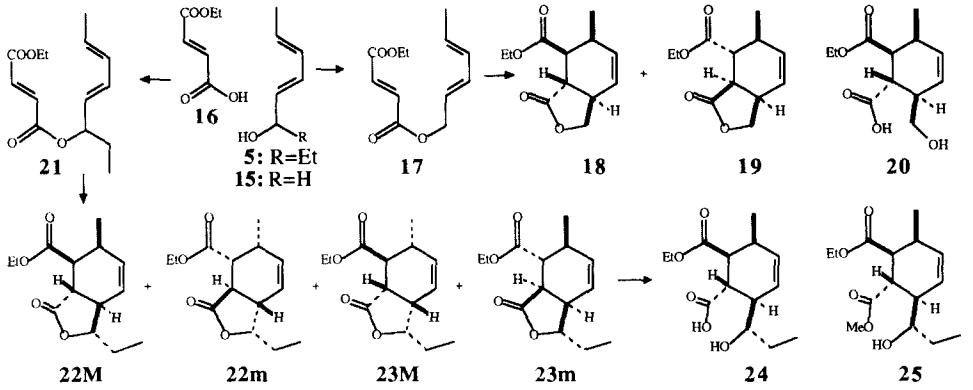


1) PhH, D, 2) Oxalyl chloride r.t., $NaBH_4$, DMF-THF, -78°C, 3) MOMCl, iPr_2NEt, 4) 7.5N aq.NaOH, D, 5) CH_2N_2, Et_2O, 0°C, 6) MsCl, Et_3N, CH_2Cl_2, 7) Li, NH_3liq, EtOH, -78°C, 8) $EtC(Me)_2COCl$, Et_3N, DMAP, CH_2Cl_2, r.t., 20h., 9) $HSCH_2CH_2SH$, $BF_3.Et_2O$, CH_2Cl_2, r.t., 10 min. 10) Ra-Ni, MeOH, 30 min.

Compound **14**,whose B-ring is saturated, corresponds to trans-tetrahydrocompactin/mevinolin type A-seco mevinic acids and was easily obtained either by reduction of **3** (1.75 mmol of the latter in 20 ml of methanol were hydrogenated for 30 min in the presence of 500 mg of Raney-nickel, 97%) or by double bond reduction of

11 followed by the same sequence of transformations as for **3.**

The Intramolecular Diels-Alder route: The potential utility of **3** in mevinic acid synthesis prompted us to explore the intramolecular variant of the [4+2] cycloaddition. Elaboration of the required (E,E,E)-undeca-2,7,9-trienoates **17** and **21** was accomplished by esterification with fumaric acid monoester **16** of sorbic alcohol for the former and dienol **5** for the latter (40 mmol of the alcohol, 51 mmol of **16**, 51 mmol of DCC, 15 mmol of DMAP, in 250 ml of CH_2Cl_2 at r.t. under argon, 100%). Thermal cyclization of **17** (0.03 M in $PhCH_3$, 100°C, 24 h) afforded the trans and cis-fused lactone-esters **18** and **19** in 78% yield and 60:40 ratio respectively. Trienoate **21** under identical reaction conditions afforded two trans-fused lactone esters **22M** and **22m** via an exo-chain *endo* addition (80%, 11:1) and two cis-fused lactone esters **23M** and **23m** via an endo-chain *exo* addition (20%, 4:1). A lipase mediated chemoselective hydrolysis[12] set the stage for the rapid synthesis of the tetrasubstituded cyclohexene derivatives **20** and **24** which have the correct substitution pattern and can further be transformed to the above cited monocyclic analogues using literature methods. The crude Diels-Alder product **18+19** (2.32 mmol, 520 mg) was subjected to enzymatic hydrolysis by employing *pig liver esterase* (800 mg), in 75 ml of phosphate buffer pH=8 and 3 ml of toluene, at 27°C for 24 h to yield 212 mg (38%) of optically enriched **20** (the trans-lactone ring opening) together with 261 mg of unreacted lactone esters. Neither lactone ring opening nor ester hydrolysis was detected after 3 days stirring of **18+19** in the same buffer solution at 27°C. Encouraged by this chemo- and diastereopreference we next examined the lactone-ester mixture obtained from trienoate **21**. Screening experiments (equal masses of the substrate and enzyme preparation in phosphate buffer) using *pig liver esterase* (PLE) and *horse liver esterase* (HLE) showed a net diastereopreference towards the trans-lactone ester opening. Subjecting the crude Diels-Alder product from **21** to enzymatic hydrolysis under the above cited conditions resulted again in the chemo (the carboethoxy group remained intact) and diastereoselective openings (only the trans lactone esters were opened). The same experiment carried under slightly different conditions (phosphate buffer pH=7 containing 10% t-BuOH, at 33°C-4h, or 27°C-16h, with either PLE or HLE) led to optically homogeneous **24** in 27% yield, characterized as its methyl ester **25**[13] and derivatized with (S)-O-acetyllactyl chloride.



The enantioselective version of this enzymatic hydrolysis as well as X-ray crystallographic studies for absolute stereochemistry determination will be published in due course.

Only five steps are required for the transformation of our target compound **3** into the A-seco mevinic acid

2 (either in its lactone or the 3,5-dihydroxy acid form) using Heathcock's procedure for compactin,[14] dihydromevinolin,[15] and monocyclic analogues (ref. 5) which consists in coupling of the optically homogeneous ketophosphonate **7** and an aldehyde derived from the hexalin moiety of compactin. The straightforward preparation of **3** from sorbic aldehyde in ten steps illustrates the potential of our methodology as an expedient formal total synthesis of A-seco mevinic acids considerably simpler than those previously reported.

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11. **3**: oil, **I.R**.(film): 3462, 2971, 2931, 2871, 1727, 1463, 1242, 1156, 1062 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.85 (3H, t, J=7.5), 0.90 (3H, t, J=7.0), 0.93 (3H, d, J=7.2), 1.16 (6H,s), 1.18-1.65 (5H, m), 1.57 (2H, q, J=7.5), 1.96 (1H, m), 2.04 (1H, m), 2.43 (1H, m), 3.62 (1H, dd, J=8.1, 10.7), 3.78 (1H, dd, J=5.7, 10.7), 4.11 (1H, dd, J=3.3, 11.6), 4.18 (1H, dd, J=4.1, 11.6), 5.55 (1H, ddd, J=1.5, 2.4, 10.0), 5.69 (1H, ddd, J=2.6, 5.0, 10.0); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 9.2, 14.3, 15.6, 19.4, 21.6, 24.6(2xMe), 30.5, 33.3, 35.6, 35.7, 37.2, 41.2, 42.9, 63.3, 63.9, 129.4, 132.1, 178.0; **C.I.M.S**.: 297(M+H, 100%), **H.R.C.I.M.S**. calc for $C_{18}H_{33}O_3$ 297.2430 found: 297.2457.
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13. **25**: oil, $[\alpha]_D$ +67 (c=1.04, $CHCl_3$) **IR**.(film): 3495, 2971, 2871, 1735, 1438, 1268, 1194, 1169, 1146, 1095, 1029, 976 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.89 (3H, d, J=7), 0.99 (3H, t, J=7.4), 1.25 (3H, t, J=7.1), 1.33 (1H, m), 1.58 (1H, m), 2.58 (1H, m), 2.69 (1H, dd, J=10.8, 11.5), 2.71 (1H, m), 3.07 (1H, dd, J=5.5, 11.5), 3.58 (1H, m), 3.71 (3H, s), 4.14 (2H, m), 5.66 (1H, dt, J=1.7, 10.1), 5.81 (1H, ddd, J=2.5, 5.2, 10.1); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 10.5, 14.1, 16.6, 24.9, 31.2, 39.2, 46.2, 46.7, 51.7, 60.5, 74.1, 124.7, 132.3, 173.3, 176.2; **C.I.M.S**.: 285(M+H), **H.R.C.I.M.S**. calc for $C_{15}H_{25}O_5$ 285.1702 found: 285.1719.
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(*Received in France* 17 *August* 1994; *accepted* 30 *August* 1994)