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Convergent Synthesis of a Key Intermediate for Hypocholesterolemic Agent 1233A, Starting from Methyl 3-Hydroxy-2-methylpropanoate and Asymmetrized *Bis*(hydroxymethyl)acetaldehyde (BHYMA*)

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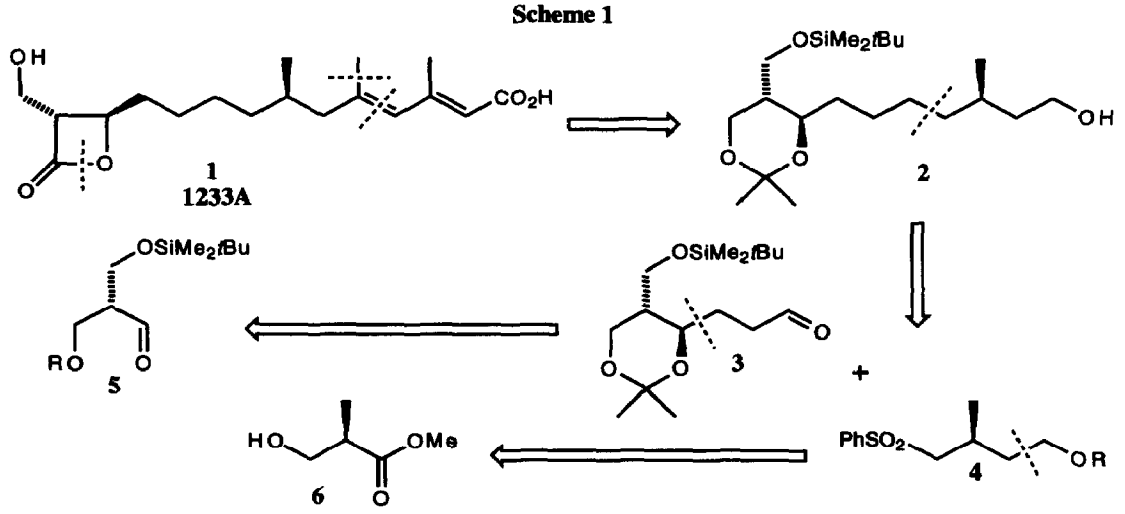
Abstract: Compound **2**, which is a known intermediate for the total synthesis of hypocholesterolemic agent 1233A **1**, has been synthesized in good overall yield through a convergent approach, employing 3-hydroxy-2-methylpropanoate **6** and BHYMA* **5** as chiral building blocks.

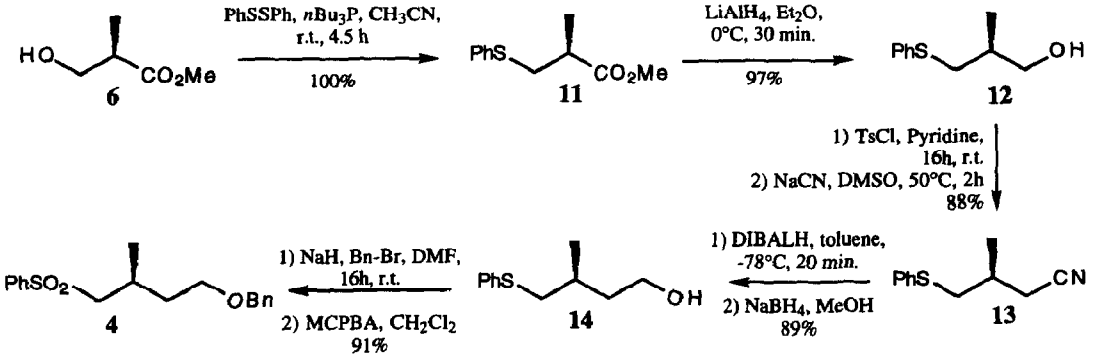
The naturally occurring β-lactone 1233A **1** (also called F-244 or L-659,699)[1] was independently isolated from three different microorganisms and was recently shown to possess a remarkable hypocholesterolemic activity through specific inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase. Four total syntheses of this pharmacologically promising compound have been accomplished to date.[1a-d] In particular, the one recently reported by Wovkulich *et al.*[1c] seems more efficient than the previous ones, exploiting an improved method for the stereoselective assemblage of the diene portion, which was attached starting from the key intermediate **2** (Scheme 1). However, the preparation of **2** suffers from the high number of steps (16), mainly due to a non-convergent approach.

Examination of compound **2** suggested that it could be assembled starting from two C-4 branched chiral

Scheme 1



Scheme 2

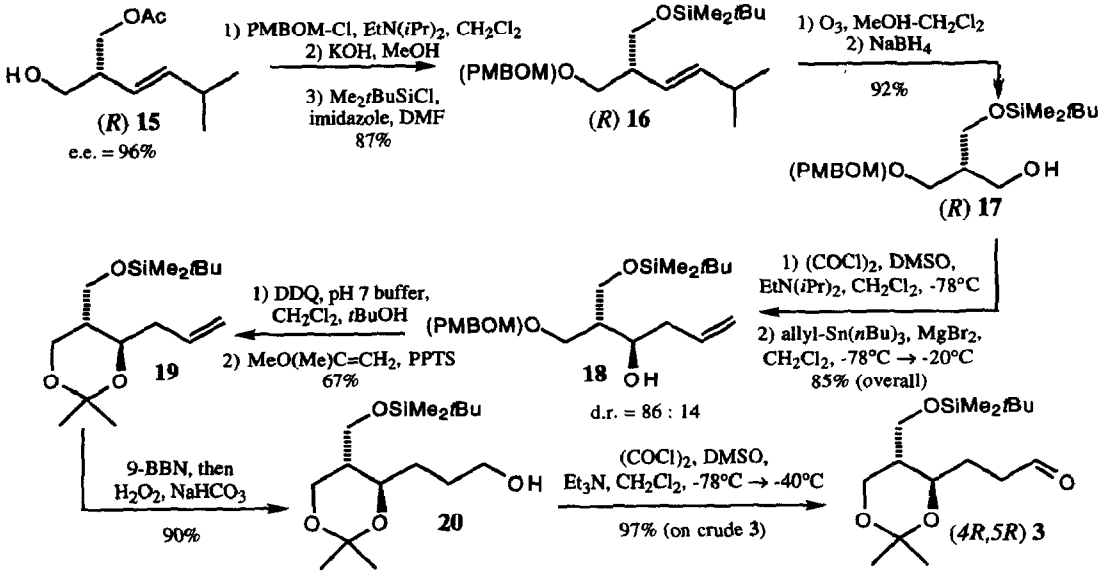


starting materials, namely (*R*) methyl 3-hydroxy-2-methylpropanoate **6**,[2] and asymmetrized *bis*(hydroxymethyl)acetaldehyde (BHYMA*) **5**. The latter represents a new chiral building block, recently made available by us in both enantiomeric forms through enzyme-mediated asymmetrization,[3] and already employed in several synthetic applications.[4] Our plan (Scheme 1) involved a Julia-Kocienski condensation[5,6] of sulphone **4** with aldehyde **3**, obtained respectively by homologation of **6** and by diastereoselective addition of a C-3 fragment to aldehyde **5**.

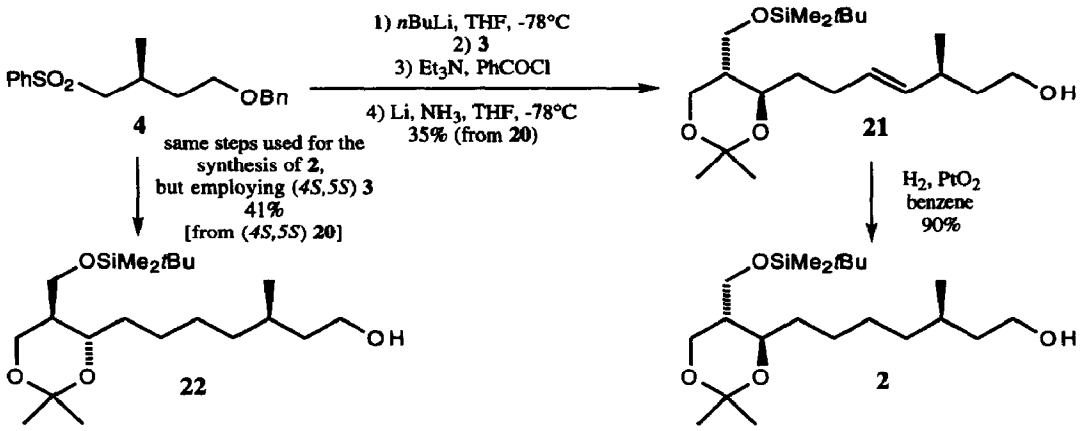
Scheme 2 shows the transformation of **6** into sulphone **4**. After substitution of the hydroxyl with a phenylthio group,[7] the other side arm of the starting building block was homologated, after ester reduction, using sodium cyanide as a $[CH_2OH]^-$ synthetic equivalent. Actually, two step reduction of the resulting nitrile **13** furnished the desired primary alcohol **14**.[8] Finally, protection as the benzyl ether and oxidation furnished sulphone **4** in good overall yield (69%, 8 steps).

Scheme 3 depicts the synthesis of aldehyde **3** from the monoacetate **15**, which was prepared in excellent

Scheme 3



Scheme 4



e.e. (96%) through enantioselective PPL catalyzed monoacylation of the corresponding diol.[3b,10] The second asymmetric centre was introduced with good stereoselectivity through the previously reported[4e] "protecting group controlled" allylation of the *bis*(hydroxymethyl)acetaldehyde (BHYMA*) derived from oxidation of alcohol **17**. Deprotection of the *p*-methoxybenzyloxymethyl group,[4c,4d,11] followed by formation of an acetonide gave **19**, which was then regioselectively hydrated at the terminal double bond position by hydroboration-oxidation.[1c] Finally Swern oxidation gave aldehyde **3** in 35% overall yield (10 steps) from monoacetate (*R*) **15**.

Coupling of aldehyde **3** with sulphone **4** (Scheme 4) proceeded without problems. On the contrary, reductive elimination of the benzoyl derivative with Na•Hg, under usual conditions,[5a-c,7] gave unsatisfactory yields of the expected alkene. Finally we found that moderate yields could be achieved by *in situ* benzoylation of the diastereomeric mixture of condensation products, followed by reduction with Li-NH_3.[5d] Under these conditions, the benzyl protecting group was also removed, giving alcohol **21** as a *ca.* 9:1 *E* : *Z* mixture. Hydrogenation of the latter afforded our target **2**, whose spectroscopic and polarimetric data were in good agreement with the previously reported ones.[1c,12] The overall yield of **2** from monoacetate **15** was 11%, and thus our synthesis compares favourably with the one previously realized by Wovkulich *et al.*[1c]

Since chiral building blocks **6**[2] and **5**[3] are easily available in both enantiomeric forms, the preparation of stereoisomers of **2** through this route can be easily accomplished. As an example we have prepared compound **22**, by coupling sulphone **4** with the enantiomer of **3** and following the same synthetic steps (Scheme 4).[12] This stereochemical versatility can be useful for the preparation of analogues of 1233A **1** having different relative configurations.

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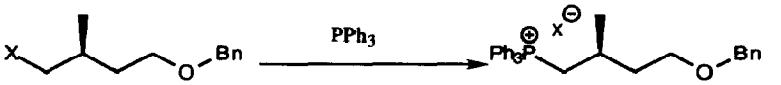
6. Preliminary attempts to use a Wittig methodology for coupling of the two fragments were hampered by unsatisfactory yields in the conversion of iodide **7** or bromide **8** into the corresponding phosphonium halides **9** and **10**.



7 : X = I
8 : X = Br

9 : X = I
10 : X = Br

7. Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett.* **1987**, *28*, 5205-5208.
8. Mosher's ester analysis (^{1}H n.m.r.) was carried out on alcohols **14** and **18** and showed no racemization.
9. Abbreviations used in this paper: PMBOM = *p*-methoxybenzyloxymethyl. PPTS = pyridinium *p*-toluenesulfonate. 9-BBN = 9-borabicyclononane. DDQ = Dichlorodicyano-*p*-benzoquinone.
10. Alcohol (*R*) **17** can be also prepared starting from (*S*) **15**, in turn available through PPL catalyzed monohydrolysis of the corresponding diacetate (see refs. 3a and 4d) . However, the overall yields have been higher starting from (*R*) **15**. The enantiomer of **18** was previously obtained through direct allylation of the crude aldehyde derived from ozonolysis of (*S*) **16** (see ref. 4c). Nevertheless, better yields are obtained by the here described two-step sequence, taking advantage of the oxidation of alcohol **17** under the modified Swern conditions developed by us (ref. 4d).
11. In order to avoid acid catalyzed hydrolysis of the Me$_2$*t*BuSi ether, the procedure described in refs. 4d and 4e was modified by using 1.25 eq. of 1M buffer solution for each eq. of DDQ.
12. The only discrepancy with ref. 1c is due to the $\underline{C}H_2$ peak at 26.89 ppm in the ^{13}C n.m.r., which was reported at 26.2 ppm. We think that a typing error could have occurred in ref. 1c. **2** and **22** were indistinguishable at t.l.c. and gave superimposable ^{1}H n.m.r. spectra. There were however slight differences in the ^{13}C n.m.r.: **2**: 98.11 (O-$\underline{C}$-O); 70.15 ($\underline{C}$H-O); 62.11,61.35,61.23 ($\underline{C}H_2$O); 41.69 ($\underline{C}$H); 40.04, 37.08, 33.51 ($\underline{C}H_2$); 29.41 ($\underline{C}$H); 29.22 ($\underline{C}H_3$); 26.89 ($\underline{C}H_2$), 25.81 [C($\underline{C}H_3$)$_3$]; 25.29 ($\underline{C}H_2$); 19.68,19.55 ($\underline{C}H_3$); 18.16 [$\underline{C}$(Me)$_3$]; -5.60 [Si($\underline{C}H_3$)$_2$]. **22**: 98.09 (O-$\underline{C}$-O); 70.20 ($\underline{C}$H-O); 62.12,61.35,61.26 ($\underline{C}H_2$O); 41.66 ($\underline{C}$H); 39.92, 37.15, 33.53 ($\underline{C}H_2$); 29.49 ($\underline{C}$H); 29.25 ($\underline{C}H_3$); 26.94 ($\underline{C}H_2$), 25.84 [C($\underline{C}H_3$)$_3$]; 25.38 ($\underline{C}H_2$); 19.71 ($\underline{C}H_3$) (2); 18.20 [$\underline{C}$(Me)$_3$]; -5.48,-5.50 [Si($\underline{C}H_3$)$_2$].

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