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Total synthesis and determination of the absolute stereochemistry of the squalene synthase inhibitors CJ-13,981 and CJ-13,982

Frederick Calo [a], Alexander Bondke [a], Jeffery Richardson [b], Andrew J. P. White [a], Anthony G. M. Barrett [a,*]

[a] Department of Chemistry, Imperial College, London SW7 2AZ, England, UK
[b] Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, Surrey GU20 6PH, England, UK

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ABSTRACT

The absolute and relative stereochemistries of the potent squalene synthase inhibitors CJ-13,981 and CJ-13,982 were determined to be 3*S*,4*S* by total synthesis of their antipodes using, as a key step, the diastereoselective alkylation of a chiral dioxolanone.

Squalene synthase (SSase) is a key enzyme in the isoprenoid pathway, which catalyzes the biosynthesis of squalene, a key cholesterol precursor, by the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) via the intermediate presqualene pyrophosphate. Specific inhibition of SSase would suppress cholesterol biosynthesis but not prevent the formation of other essential non-sterol products such as ubiquinone, dolichol, isopentenyl *t*-RNA and prenylated proteins and therefore represents an attractive target for pharmaceutical discovery.[1]

In 2001, Pfizer scientists in Nagoya isolated two new SSase inhibitors, CJ-13,981 (**1**) and CJ-13,982 (**2**), from the fermentation broth of an unidentified fungus (CL15036) and identified their structures by FAB-MS and NMR analyses (Fig. 1). CJ-13,981 (**1**) and CJ-13,982 (**2**) inhibited human liver microsomal SSase with IC_{50} values of 2.8 and 1.1 μM, respectively.[2] However, their relative and absolute stereochemistries were not determined although their optical rotations were reported.[3]

As part of our research on the total synthesis of alkyl citrate natural products,[4] we sought to determine the full stereochemistries of **1** and **2** by the total synthesis of two of the four possible stereoisomers. Arbitrarily, we set the C-3 stereochemistry as *R*. The retrosynthetic analysis for both the 3*R*,4*S* and 3*R*,4*R* 15-alkene stereoisomers is shown in Scheme 1.

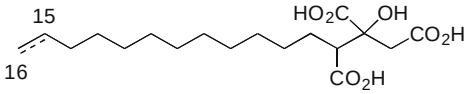
The triacids **3** and **4** should be available from the precursors **5** and **6** by saponification. In turn, the dioxolanones **5** and **6** should be available from aldehydes **9** and **10** by Wittig reaction, hydrogenation and elimination of the benzyloxy substituent. The key aldehydes **9** and **10** should be synthesized from oxazolidinone **13,** respectively, by either a *syn*- or an *anti*-aldol reaction, dioxolanones **11** and **12** formation and Seebach Self Retention of Stereocentre (SRS) alkylation using *tert*-butyl bromoacetate.

Dioxolanone **11** was recently applied in the total synthesis of citrafungin A[4b] and we decided to apply the same strategy to elaborate its diastereoisomer **12** starting from **13** by using an *anti*-aldol reaction. Contrary to our expectation, attempted *anti*-aldol reactions of **13** with propenal in the presence of the Lewis acids *n*-Bu_2BOTf-Et_2AlCl,[5] $MgCl_2$,[6] *c*-$(C_6H_{11})_2BCl$,[7] or $MgBr_2{\cdot}OEt_2$[6] either failed or gave intractable mixtures of diastereoisomers. However, by changing the electrophile to cinnamaldehyde, the Evans $MgBr_2{\cdot}OEt_2$ catalyzed *anti*-aldol reaction proceeded in 84% yield after TFA-mediated desilyation (Scheme 2).

The resultant secondary alcohol **14** was protected[8] as the acetate **15** (96%), the structure of which was confirmed by X-ray crystallography. Ozonolysis using a dimethyl sulfide work-up[9] and subsequent Pinnick oxidation gave the corresponding carboxylic acid which was esterified using diazomethane[10] to give the methyl ester **16**. Triple oxazolidinone, methyl ester and acetate hydrolysis using lithium hydroxide and hydrogen peroxide gave diacid **17**, which was converted into the *cis*-dioxolanone **12** using Hoye acetalization.[11] The structure of **12** was confirmed by NOESY NMR.

Attempted acetalization of **17** using a 4-toluenesulfonic acid-catalyzed condensation reaction[12] gave an inseparable 1:1 mixture of **12** and its *trans*-isomer. Seebach SRS alkylation[4] of dioxolanone **12** by double deprotonation using lithium hexamethyldisilazide in DMF at −70 °C followed by addition of *t*-butyl bromoacetate gave exclusively the dioxolanone **18** in 65% yield.

Diazomethane esterification of carboxylic acids **18** and **19**[4b] gave the corresponding methyl esters, which were subjected to benzyl ether hydrogenolysis and Dess–Martin oxidation[13] to give aldehydes **9** and **10**, both in 91% yield over the three steps. Wittig olefination using *n*-BuLi and $BrPh_3PCH_2(CH_2)_8OBn$[14] (**20**), respec-



CJ-13,981 (**1**) (15,16-olefin)
CJ-13,982 (**2**) (15,16-dihydro)

Figure 1. Structures of CJ-13,981 (**1**) and CJ-13,982 (**2**).

* Corresponding author. Tel.: +44 0 207 594 5767; fax: +44 0 207 594 5805.
E-mail address: agmb.office@imperial.ac.uk (A.G.M. Barrett).

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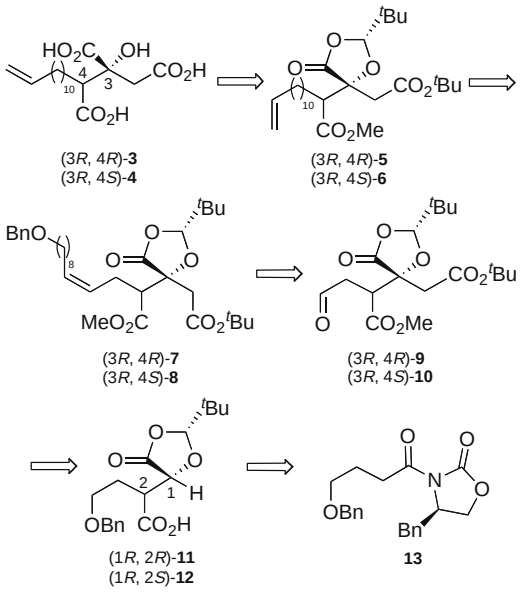
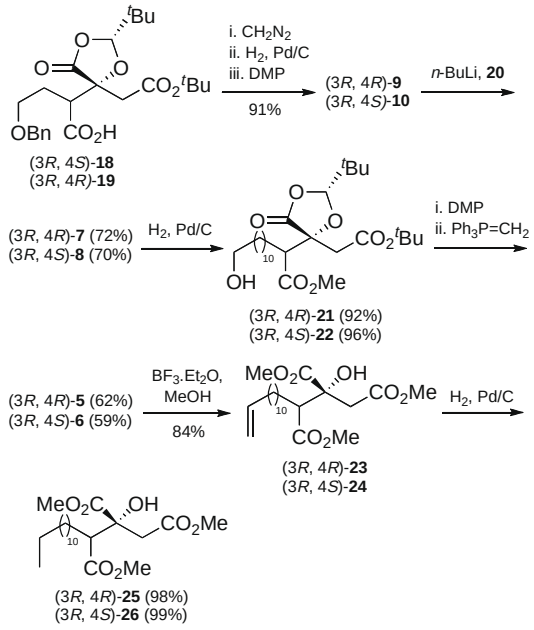
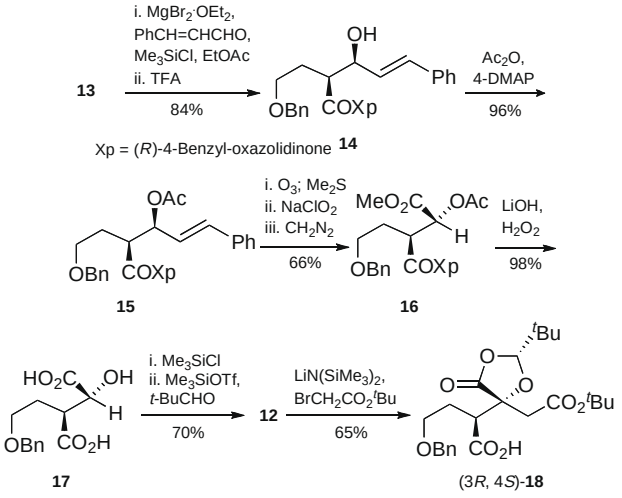


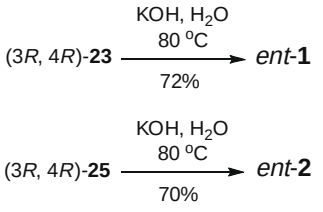
Scheme 1. Retrosynthetic analysis.



Scheme 3. Synthesis of triesters **23–26**.



Scheme 2. Synthesis of dioxolanone **18**.



Scheme 4. Synthesis of *ent*-**1** and *ent*-**2**.

tively, gave *cis*-alkenes **7** and **8**, which were hydrogenated over palladium on carbon in 66% and 67% yields (two steps) for each diastereoisomer (Scheme 3). Sequential Dess–Martin oxidation and Wittig olefination gave alkenes (3*R*,4*R*)-**5** and (3*R*,4*S*)-**6** in 62% and 59% yields, respectively, over the two steps.

It is noteworthy in this sequence that the dioxolanone was used as a protecting group for the α-hydroxy acid as well as the stereocontrol element in the Seebach alkylation reaction. Dioxolanone ring opening was effected by reflux in methanol containing boron trifluoride etherate[15] in a sealed tube giving the trimethyl esters **23** and **24** (84%) which were hydrogenated over palladium on carbon to give esters, **25** and **26**, respectively.

At this stage, the ^{1}H NMR spectra of **23** and **25** exhibited high similarity to those of the natural products **1** and **2** having three extra methyl ester singlets and are distinct from the corresponding diastereoisomers **24** and **26**.

Saponification of both **23** and **25** using potassium hydroxide at 80 °C[16] in H_2O gave, after purification on reverse phase silica, *ent*-**1** and *ent*-**2** (Scheme 4). In contrast, attempted saponification of **24** and **26** resulted in extensive decomposition. All the analytical data for the synthetic samples of *ent*-CJ-13,981 (**1**) and *ent*-CJ-13,982 (**2**) matched with those reported for the natural products except for the signs of the optical rotations.

In conclusion, we report the enantioselective syntheses of *ent*-**1** and *ent*-**2** and the determination of the absolute and relative stereochemistries of both natural products as 3*S*, 4*S*.

Acknowledgements

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Supplementary data

Procedures for the synthesis of new compounds, along with characterization data, spectra and the X-ray crystallographic structure for **15** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.121.

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