Total Synthesis and Stereochemical Assignment of the Quinquecyclopropane-Containing Cholesteryl Ester Transfer Protein Inhibitor U-106305

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Recently, Upjohn scientists have reported the isolation of the unusual metabolite U-106305 (**1**) from the fermentation broth of *Streptomyces sp.* UC 11136.[1] The compound is structurally remarkable being graced with six cyclopropane rings, five of which are contiguous. U-106305 (**1**) is a potent *in vitro* inhibitor of the cholesteryl ester transfer protein (CETP) reaction, thus being of potential application in the prevention of arteriosclerosis.[2] Extensive NMR studies of the fatty amide side chain were consistent with the assignment of all of the alkene units as *trans* and all of the cyclopropane rings *trans*-disubstituted. However, the authors did not determine the absolute stereochemistry of any chiral center. In consequence there are 64 possible stereoisomeric structures for this exquisite natural product.

U-106305 (**1**) shows a striking similarity to the potent antifungal agent FR-900848 (**2**) which was isolated from the fermentation broth of *Streptoverticillium fervens*.[3] The full structure and absolute stereochemistry of FR-900848 (**2**) were recently determined by our group.[4] Additionally, we have recently reported the total synthesis of FR-900848 (**2**) thereby confirming its relative and absolute stereochemistry.[5] Since all the cyclopropane units of FR-900848 (**2**) are located on the same face of an all-*anti* carbon backbone, it appears reasonable to assume that the same (or similar) enzyme is involved in the biosynthesis of each cyclopropane entity. The Upjohn group have shown that all six cyclopropane methylene carbons of U-106305 (**1**) are biosynthetically derived from methionine.[1] Finally, it should be noted that the organisms producing both U-106305 (**1**) and FR-900848 (**2**) are related. In consequence of all these factors, we considered that both U-106305 (**1**) and FR-900848 (**2**) should be isostructural and that the absolute stereochemistry of U-106305 should be represented as stereoisomer **3**. Herein we report the first total synthesis of U-106305 (**3**), which establishes this structural hypothesis to be correct. The synthesis additionally underscores the versatility of Charette asymmetric cyclopropanation[6] in the synthesis of ter- and quinquecyclopropane arrays.

We have synthesized **3**, using a bi-directional approach to assemble the C_2-symmetrical quinquecyclopropane unit **9** using methodology as for FR-900848 (**2**) (Scheme 1).[5] Charette cyclopropanation[6] of the readily available 2(*E*)-butene-1,4-diol

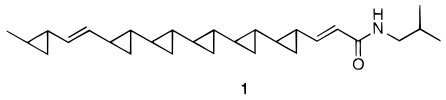

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Figure 1.

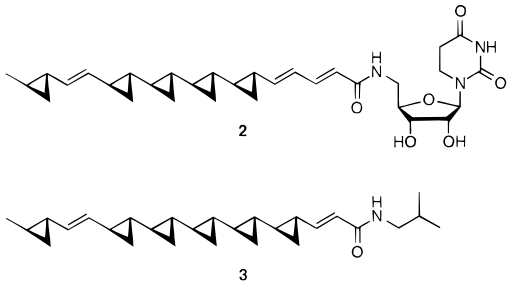

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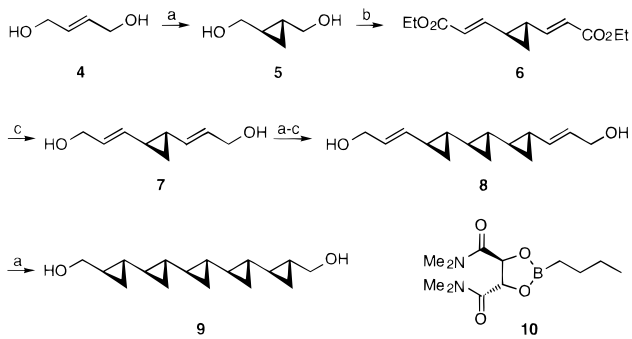
Figure 2.

Scheme 1. Synthesis of the Quinquecyclopropane **9**[a]



[a] (a) **10**, 4 Å molecular sieves, $Zn(CH_2I)_2$·DME, CH_2Cl_2, −40→25 °C, 83−91%. (b) Dess-Martin periodinane, pyridine, CH_2Cl_2, or DMSO, 25 °C; PPh_3, ca. 10 °C; $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Me$, 75−81%. (c) DIBAL-H, CH_2Cl_2, hexanes, −78 °C, 96−97%. Reactions described by a single letter were carried out in a one-pot sense without isolation of intermediates.

4[7] using pre-formed $Zn(CH_2I)_2$·DME and the chiral dioxaborolane **10** gave **5** in excellent yields. This synthesis is significantly easier than the literature synthesis[8] via the resolution of *trans*-1,2-cyclopropanedicarboxylic acid and subsequent reduction. The enantiomeric purity of **5** was variable being 74% and 89% ee respectively using 1.10 and 2.10 equiv of **10**.[9] Dess−Martin oxidation[10] of the diol **5** (81% ee) proceeded smoothly and the resultant volatile dialdehyde was directly converted into the diester **6** [96%, (*E*,*E*):(*E*,*Z*) = 28:1] by olefination with $Ph_3P{=}CHCO_2Et$. Much to our delight, fractional recrystallization of **6** was especially efficient in enriching the material in the required enantiomer. Thus recrystallization from Et_2O:petrol

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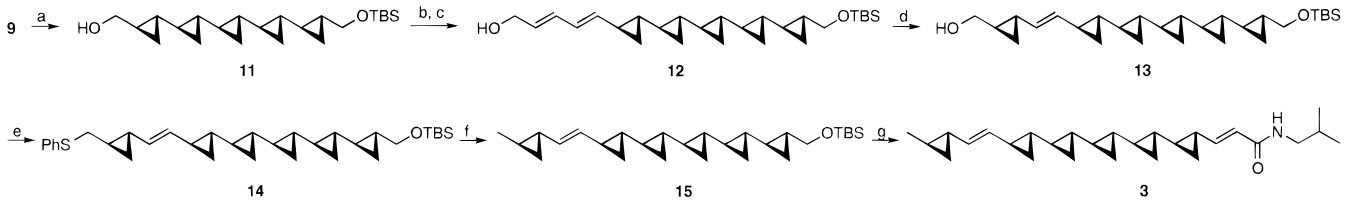
(11) Crystal data for **9**: $C_{17}H_{26}O_2$, $M = 262.4$, monoclinic, space group $P2_1$, $a = 5.221(1)$ Å, $b = 8.912(1)$ Å, $c = 16.514(1)$ Å, $\beta = 98.03(1)°$, $V = 760.9(1)$ Å^3, $Z = 2$, $D_c = 1.15$ g cm^{-3}, μ(Cu Kα) = 5.7 cm^{-1}, $F(000) = 288$. A clear platy ribbon of dimensions 0.80 × 0.23 × 0.02 mm was used. Data were measured on a Siemens P4/RA diffractometer with Cu Kα radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full-matrix least squares based on F^2 to give $R_1 = 0.042$, $wR_2 = 0.112$ for 1231 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 125°$] and 180 parameters.

(12) Büchel, K. H.; Conte, A. *Chem. Ber.* **1967**, *100*, 1248−1251.

(13) Obtained by heating 2-chloro-*N*-isobutylacetamide and triphenylphosphine to 150 °C.

S0002-7863(96)01399-6 CCC: $12.00

Scheme 2. Assembly of U-106305 **3**[a]



[a] (a) TBSCl, imidazole, CH_2Cl_2, 25 °C, 75% calcd at 78% conversion. (b) Dess-Martin periodinane, pyridine, DMSO, 25 °C; PPh_3, 25 °C; (*E*)-$(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH, DBU, 25 °C, 88%. (c) DIBAL-H, CH_2Cl_2, hexanes, −78 °C, 95%. (d) **10**, 4 Å molecular sieves, $Zn(CH_2I)_2{\cdot}DME$, CH_2Cl_2, −50→25 °C, 72%. (e) *N*-(phenylsulfenyl)succinimide,[12] PBu_3, C_6H_6, 25 °C, 91%. (f) Raney nickel, THF, 25 °C, 44%. (g) TBAF, THF, 25 °C; DMSO, pyridine, 25 °C; Dess-Martin periodinane, 25 °C; PPh_3, ca. 15 °C; $Cl^-Ph_3P^+-CH_2CONHCH_2{}^iPr$,[13] DBU, 25 °C, 91%. Reactions described by a single letter were carried out in a one-pot sense without isolation of intermediates.

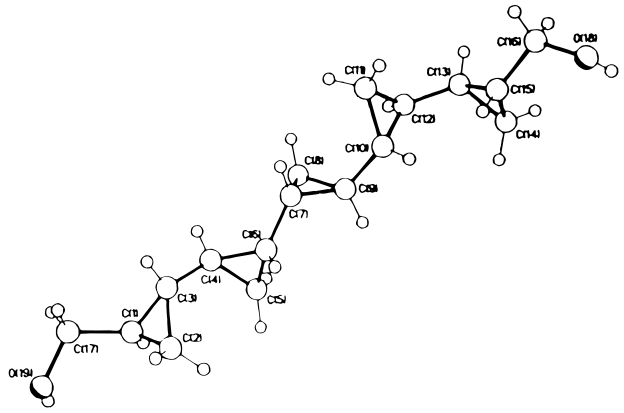


Figure 3. X-ray structure of the quinquecyclopropane **9**. The X-ray structure of **9** shows the molecule to have an extended geometry with four of the five cyclopropyl rings oriented to give an approximately uniform helix. The H−C−C−H torsional geometries about the C(3)−C(4), C(6)−C(7), and C(9)−C(10) bonds are all *gauche* with angular rotations of −61, −60 and −50°, respectively. This sequence is broken by a reversal of the sign of rotation (+50°) about the bond [C(12)−C(13)] linking the fourth and fifth cyclopropyl ring.[11]

ether gave first the racemic (*E*,*E*)-diester **6** (17%) and subsequently enantiomerically pure (*E*,*E*)-diester **6** (75%). The structures of both enantiomerically pure and racemic forms of (*E*,*E*)-diester **6** were confirmed by X-ray crystallography.

Reduction of **6** provided the bis(allylic alcohol) **7** which was doubly cyclopropanated, again using Charette methodology,[6] to produce the corresponding tercyclopropanedimethanol. Subsequent one-pot oxidation−Wittig olefination followed by DIBAL-H reduction gave the dienediol **8** in 70% yield from **7**. Double Charette cyclopropanation[6] of diene **8** afforded the quinquecyclopropane **9**. It should be noted that all the isolated intermediates in the sequence from **6** to **9** are crystalline compounds, thus facilitating the removal of any traces of undesired stereoisomers formed in the cyclopropanation reactions. The structure of the quinquecyclopropane **9** was confirmed by X-ray analysis and is shown in Figure 3.

Diol **9** was desymmetrized by silylation which gave the mono-TBS ether **11** (58%) in addition to unreacted starting material **9** (22%) and the di-TBS ether (19%) both of which were recycled. Dess−Martin oxidation, Wadsworth−Emmons homologation, and DIBAL-H reduction, gave the dienol **12**. Charette cyclopropanation of **12** proceeded with excellent stereoselectivity to give the hexacyclopropane **13**. Deoxygenation of alcohol **13** was achieved via conversion[14] into the phenyl sulfide **14** and Raney nickel mediated desulfurization. A comparable strategy was employed in our recent synthesis of FR-900848 (**2**).[5] Much to our relief, desulfurization proceeded readily to provide **15**, albeit in modest yield (44%). The synthesis of U-106305 (**3**) was completed by desilylation, oxidation to the aldehyde, and Wittig olefination to introduce the unsaturated isobutylamide. All these reactions proceeded effectively in a one-pot procedure to give **3** in 91% yield as a crystalline solid. The synthetic material was identical in all respects with an authentic sample of U-106305.[15] All these results clearly establish the full structure and stereochemistry of U-106305 (**3**). Further studies on related multiple cyclopropane systems will be reported in due course.

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Supporting Information Available: Tables of X-ray data for compound **9** and ^1H NMR, ^{13}C NMR, CD, and chiral HPLC results for **3** and authentic U-106305 (12 pages). See any current masthead page for ordering and Internet access instructions.

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(15) By ^1H NMR, ^{13}C NMR, $[\alpha]_D$, CD, UV, chiral HPLC, mp, and mixed mp.