Enantioselective Total Synthesis of (+)-U-106305

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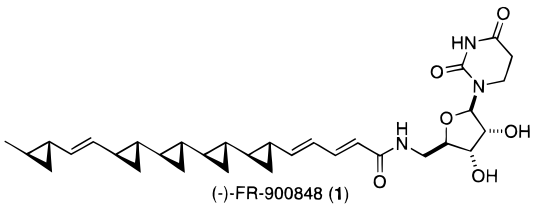
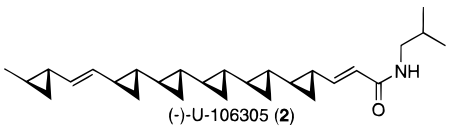
Received June 10, 1996

Two structurally intriguing natural products have been recently isolated from fermentation broths. FR-900848 (**1**),[1] a natural product which shows potent activity against filamentous fungi contains four contiguous cyclopropane rings and has been recently synthesized by Barrett[2,3] and Falck.[4] More recently, U-106305 (**2**),[5] a natural product that was shown to be a potent inhibitor of the *in vitro* cholesteryl ester transfer protein reaction, was isolated from fermentation broth of *Streptomyces* sp. UC 11136. On the basis of extensive NMR studies, the structure

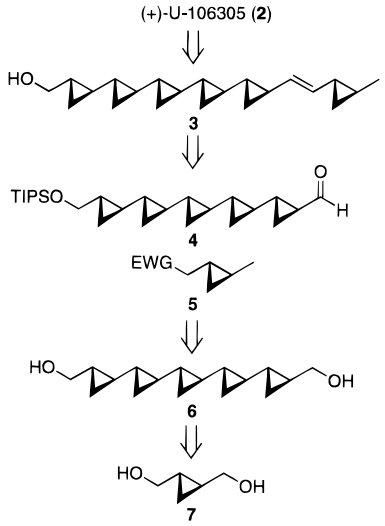




of this product was postulated to be one of the 64 possible *all-trans* isomers. It was shown to possess six cyclopropane rings, five of which are contiguous. In this paper, we report the first total synthesis of (+)-U-106305 that confirms the relative and absolute stereochemistry of the natural product. The synthesis relies heavily on the enantioselective cyclopropanation reaction developed in our laboratories[6] and on a new olefination procedure to produce the *trans*-1,2-dicyclopropylalkene.

Our retrosynthetic analysis is depicted in Scheme 1. The unsaturated amide can be prepared at a late stage in the synthesis by a standard Horner−Emmons−Wadsworth olefination reaction. We elected to elaborate the right end of U-106305 using an olefination reaction between a protected aldehyde (**4**) and a suitable precursor (**5**). Aldehyde **4** can arise from diol **6**, efficiently accessible by a bidirectional chain synthesis. The

Scheme 1



pentacyclopropane diol **6** could be constructed by two double-cyclopropanation reactions from known *trans*-1,2-cyclopropyldimethanol (**7**).

The synthesis of the U-106305 is illustrated in Scheme 2. The known diol **7**[7] was oxidized with PDC (pyridinium dichromate), and the dialdehyde was submitted to the Horner−Emmons−Wadsworth olefination followed by DIBAL-H ($(iBu)_2AlH$) reduction to produce diol **8** as a single isomer after chromatography.[8] The first enantioselective double cyclopropanation was smoothly accomplished by treating the bis(allylic alcohol) with 4.4 equiv of $Zn(CH_2I)_2$·DME and 2.2 equiv of the dioxaborolane-derived chiral ligand. Examination of the crude ^{13}C NMR revealed that a 10:1 mixture of diastereomers were produced in this process, which indicates that the cyclopropanation proceeded in *ca.* 91% ee. The bidirectional chain homologation was achieved as described before to afford the bis(allylic alcohol) **10** as a single isomer after purification. Again, the asymmetric double cyclopropanation proceeded as expected to afford the pentacyclopropanediol **6** in quantitative yield. The crude ^{13}C NMR indicated that the major isomer was contaminated with *ca.* 10% of two other unseparable isomers. The *all-syn* stereochemistry of the pentacyclopropanediol **6** was unambiguously established by X-ray crystallography.[9]

With the pentacyclopropanediol **6** in hand, we were than able to pursue several ways to elaborate the right end of U-106305 (**2**). A Julia olefination[10,11] between the monoaldehyde **4** and the benzothiazoylsulfone **12** was thought to be a good choice for the elaboration of the right end of U-106305. The α-anion of the sulfone should be stabilized by the donating ability of the benzothiazoyl group, thus preventing the cyclopropane opening that could lead to open products or partial racemization. Since there were no precedents for such coupling between two saturated alkyl moieties, a model study was undertaken to optimize the *E*:*Z* ratio in that reaction. A number of bases were

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(2) (a) Barrett, A. G. M.; Kasdorf, K.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1781−1782. (b) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1783−1784. (c) Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc., Chem. Commun.* **1995**, 355−356. (d) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 407−408. (e) Barrett, A. G. M.; Kasdorf, K.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 649−650. (f) Barrett, A. G. M.; Kasdorf, K.; Tustin, G. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1143−1144. (g) Barrett, A. G. M.; Kasdorf, K. *J. Chem. Soc., Chem. Commun.* **1996**, 325−326. (h) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J. *J. Org. Chem.* **1996**, *61*, 3280−3288.

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(4) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096−6097.

(5) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629−10634.

(6) (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651−2652. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081−1083.

(7) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013−12026.

(8) Barrett has recently used a similar bidirectional approach involving the bis(cyclopropanation) of a related bis(allylic alcohol) using the dioxaborolane-mediated asymmetric cyclopropanation as the key step for the elaboration of the tetracyclopropyl chain (ref 2g).

(9) The ORTEP drawing of **6** is provided in the Supporting Information.

(10) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336−357. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856−878.

(11) For recent applications of this reaction, see: (a) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285−296. (b) Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996**, 652−666.

S0002-7863(96)01942-7 CCC: $12.00

Scheme 2

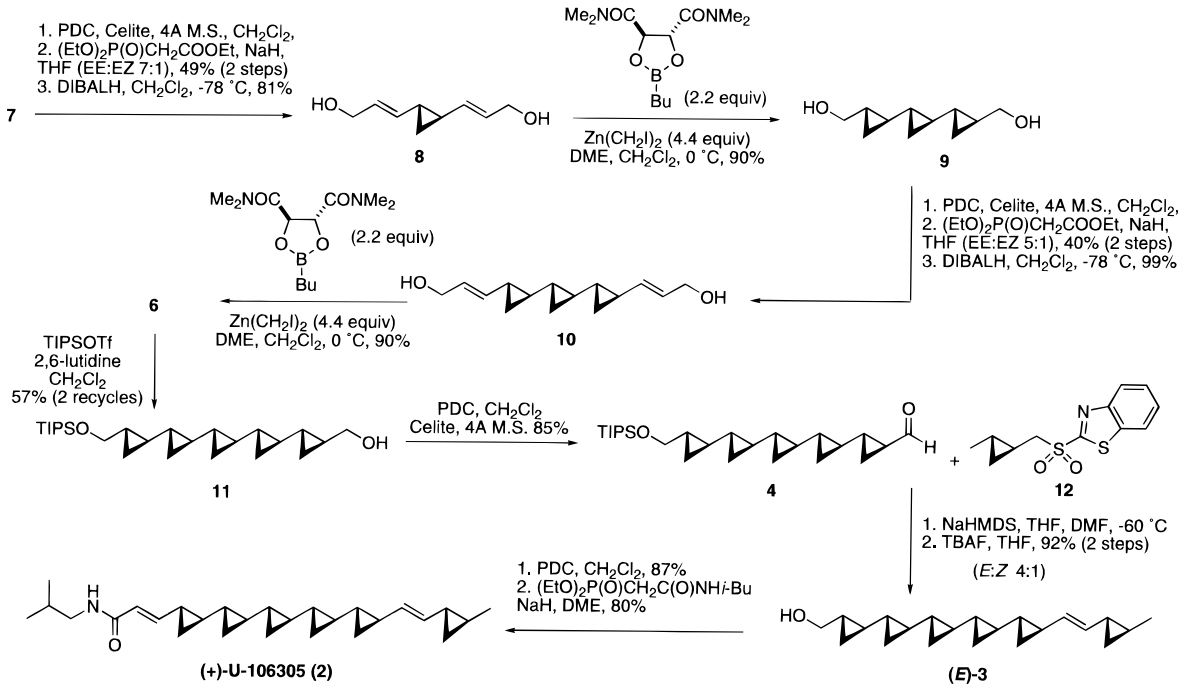
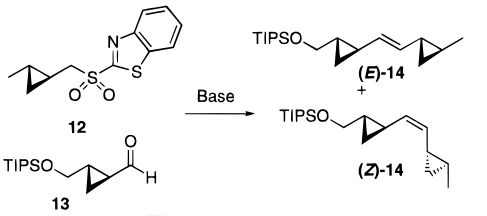


Table 1. Optimization of the Olefination Reaction



Entry	Conditions[a]	Ratio (*E*:*Z*)[b]
1	NaHMDS, THF	1.1 : 1
2	NaHMDS, DME	2.4 : 1
3	NaHMDS, DMF	3.5 : 1
4	KHMDS, THF	1.2 : 1
5	KHMDS, Toluene	1 : 3.7
6	NaHMDS, Et_2O	1 : 7.7
7	NaHMDS, Toluene	1 : 10
8	NaHMDS, CH_2Cl_2	1 : 10

[a] The NaHMDS was used as a 1.0 M solution in THF and KHMDS as a 1.0 M solution in toluene. [b] The ratios were determined by 400 MHz ^{1}H NMR, and the yields in all the cases were >90%.

added to a mixture of the benzothiazoylsulfone **12** and aldehyde **13** at −78 °C in various solvents. The nature of the solvent, counterion, and temperature were found to have a profound impact on the *E*:*Z* ratio (Table 1). A 3.4:1 mixture of *E* and *Z* isomers were obtained in quantitative yield when NaHMDS was added to a mixture of aldehyde **13** and sulfone **12** in DMF at −60 °C (1 h). Quite remarkably, the *E*- or the *Z*-isomer (**14**) can be obtained very efficiently simply by changing the solvent of the reaction (entries 3 and 6).[12] Furthermore, no isomerization or ring-opening product was observed in the process.

With these results in hand, the synthesis of U-106305 was then completed. Gratifyingly, a 4.4:1 mixture of *E*:*Z* was obtained when a solution of NaHMDS in THF was added to a solution of sulfone **12** and aldehyde **4** in DMF. The desired alcohol **3** was isolated in 92% yield for the two steps after desilylation. PDC oxidation and Horner−Emmons−Wadsworth olefination with diethyl ((*N*-isobutylcarbamoyl)methyl)phosphonate[13] produced (+)-U-106305. The synthetic and natural material were identical in all respects (^{1}H NMR, ^{13}C NMR, HPLC, HRMS) except that the sign of the optical rotation of the synthetic material was opposite to that of the natural material.[14] This therefore confirms the relative and absolute stereochemistry of this natural product.

The synthesis of (+)-U-106305 was accomplished in 14 steps (*ca.* 5% overall yield) from alcohol **7** and is suitable for obtaining large quantities of this material. It also clearly illustrates the power of the reagent-based asymmetric cyclopropanation reaction developed in our laboratories. Furthermore, the final olefination reaction, occurring without opening or scrambling of the cyclopropane stereochemistry, significantly simplifies the synthesis of this class of compounds. Further work is in progress to evaluate the biological relevance of the stereochemistry of these polycyclopropane natural products.

Acknowledgment. This research was supported by the NSERC (Canada), Petroleum Research Fund, administered by the ACS, an Alfred P. Sloan Research Fellow, Merck Frosst Canada, FCAR (Québec), Eli Lilly, and the Université de Montréal. H.L. would like to thank the NSERC for a 1967 Science and Engineering scholarship. We are also grateful to the Centre Régional de Spectroscopie RMN for their assistance in carrying out NMR experiments and the Laboratoire de Diffraction des Rayons-X de l'U de M. We also thank Dr. M. S. Kuo (Parmacia & Upjohn Laboratories) for providing us with a sample and characterization data of natural U-106305 and Prof. Jim Leahy (Berkeley) for helpful discussions concerning the Julia reaction.

Supporting Information Available: Experimental procedures, characterization data, ORTEP drawing of **6**, and copies of ^{1}H and ^{13}C NMR spectra of all the compounds (41 pages). See any current masthead page for ordering and Internet access instructions.

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(12) A number of other olefination methods were surveyed, but they all failed to give any noticeable amount of the desired product.

(13) Landor, P. D.; Landor, S. R.; Odyek, O. *J. Chem. Soc., Perkin Trans. 1* **1977**, 93−95.

(14) Natural U-106305: $[\alpha]_D$ −270° (*c* 0.27, $CHCl_3$) and synthetic U-106305: $[\alpha]_D$ +297° (*c* 1.02, $CHCl_3$).