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Asymmetric Total Synthesis and Formal Total Synthesis of the Antitumor Sesquiterpenoid (+)-Eremantholide A

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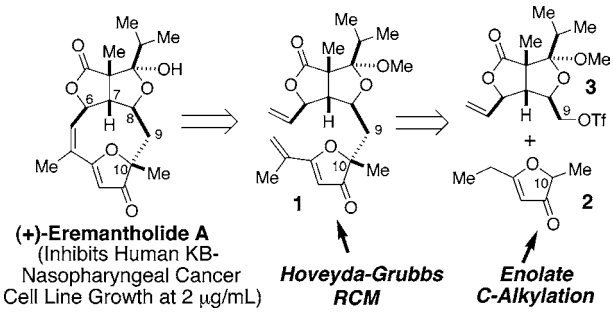
ABSTRACT



A new asymmetric total synthesis of (+)-eremantholide A is reported in which a Hoveyda–Grubbs ring-closing metathesis (RCM) reaction is used to assemble the nine-membered oxonin ring, and an enolate alkylation between the 3(2*H*)-furanone 2 and O-triflate 3 is exploited for C(9)–C(10) bond construction. An Evans asymmetric aldol reaction and a Sharpless asymmetric epoxidation served to stereoselectively install the C(6), C(7), and C(8) stereocenters of the target structure.

(+)-Eremantholide A is a structurally novel tumor-inhibiting germacranolide obtained from *Eremanthus elaeagnus*, a rare woody composite found in Brazil.[1] Ever since its initial discovery in 1975 by Le Quesne and Brennan, (+)-eremantholide A has elicited significant synthetic interest[2] on account of its pronounced antitumor effects against human KB nasopharyngeal carcinoma[1,3] and its architecturally intriguing structure which provides a significant challenge for asymmetric total synthesis.

Notwithstanding (+)-eremantholide A first being isolated more than 30 years ago, the signal transduction pathways and genes that it controls (within human cancer cells) remain undefined,[4] and its potential for inhibiting the growth of xenografted solid human tumors in mice has yet to be demonstrated. In connection with our own proposed studies in this area and to facilitate future analogue development, we recently opted to devise a new asymmetric total synthesis of (+)-eremantholide A and, herein, now report success in this venture with a route that exploits high-dilution ring-closing metathesis (RCM) to close the highly strained nine-membered oxonin ring present within the target.

Our retrosynthetic planning for (+)-eremantholide A (Scheme 1) disassembled the molecule across its C(4)−C(5)

(1) (+)-Eremantholide A isolation, structure determination, and initial antitumor evaluation: (a) Raffauf, R. F.; Huang, P.-K. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975**, *97*, 6884. (b) Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1572.

(2) For past total syntheses of (+)-eremantholide A, see: (a) Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682. (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179.

(3) Hladon, B.; Twardowski, T. *Pol. J. Pharmacol. Pharm.* **1979**, *31*, 35.

(4) Although 15-acetoxy-eremantholide B inhibits NF-κB at 5 μM in Jurkat T cells, (+)-eremantholide A does not inhibit this target at the concentrations needed to inhibit cancer cell growth. See: Rüngeler, P.; Castro, V.; Mora, G.; Gören, N.; Vichnewski, W.; Pahl, H. L.; Merfort, I.; Schmidt, T. J. *Bioorg. Med. Chem.* **1999**, *7*, 2343.

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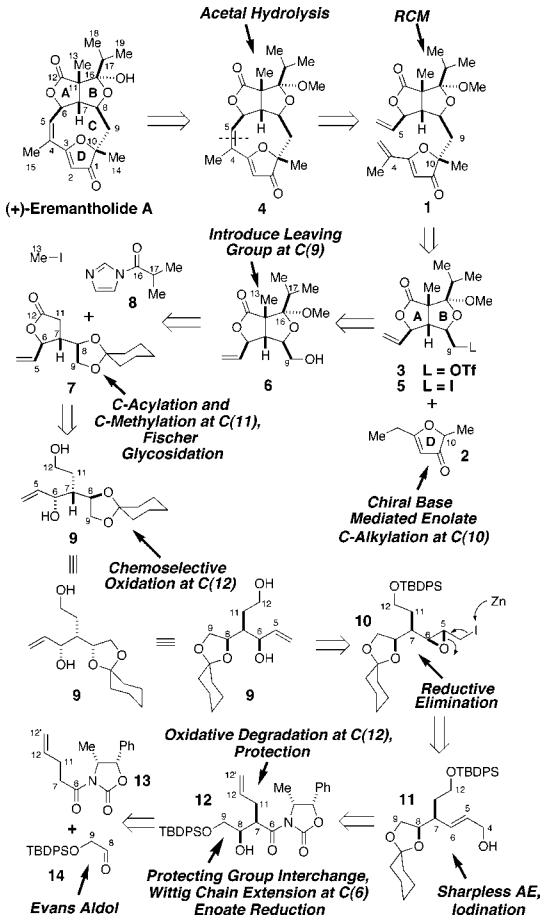
Scheme 1. Our Retrosynthetic Analysis of (+)-Eremantholide A



trisubstituted olefin and opted to construct its synthetically challenging nine-membered oxonin ring via RCM. For C(10) quaternary stereocenter installation, we proposed to react the O-triflate **3** or iodide **5** with the "chiral" lithium enolate obtained from **2**[5] by kinetic deprotonation with lithium bis-[(*S*)-α-methylbenzylamide] (or its (*R*)-optical antipode),[6] in the hope that such a device would permit a diastereoselective union between the AB- and D-ring fragments. Intermediates **3** and **5** would themselves be prepared from alcohol **6**, which potentially would be fashioned from the lactone **7** by enolate C-acylation/C-methylation and Fischer glycosidation with MeOH.

Our preferred strategy for securing the desired butyrolactone **7** would entail us chemoselectively oxidizing the diol **9** and assembling the latter from iodo-epoxide **10** by reductive elimination. Compound **10** would be fashioned from the allylic alcohol **11** by Sharpless asymmetric epoxidation (AE)[7] and iodination. The C(7) and C(8) stereocenters of **11** would be installed through an Evans asymmetric aldol reaction[8] between **13** and **14**[9] which would yield **12**. Theoretically, the conversion of **12** into **11** would require functional group interchange at O(8), O(9), and C(6), oxidative cleavage of the C(12) alkene, reduction of the product aldehyde, and introduction of a TBDPS protecting group on the newly elaborated oxygen atom. Thereafter, Wittig chain extension of a suitable C(6) aldehyde and enoate 1,2-reduction would furnish the desired allylic alcohol **11**.

The synthesis of lactone **7** (Scheme 2) commenced with a low-temperature Evans aldol reaction[8] between oxazolidinone **13** and aldehyde **14**,[9] which delivered a single *syn*-aldol adduct **12** in 81% yield. Reductive removal of the chiral auxiliary from **12** with $LiBH_4$ in MeOH/THF furnished the diol **15** which underwent O-desilylation with KF in aqueous DMF to provide the triol **16** in 71% combined yield. Although *n*-Bu_4NF also proved effective at cleaving the TBDPS group from **15**, the problems it caused in the purification of **16** made KF the reagent of choice for this operation. Next, we selectively protected the terminal 1,2-diol grouping in **16** to allow the C(6) primary alcohol to be selectively manipulated. For this, O-cyclohexylidenation with cyclohexanone and *p*-TsOH[10] proved optimal; the desired alcohol **17** was formed in 75% yield without contamination of the crude reaction mixture with any of the 1,3-dioxane.

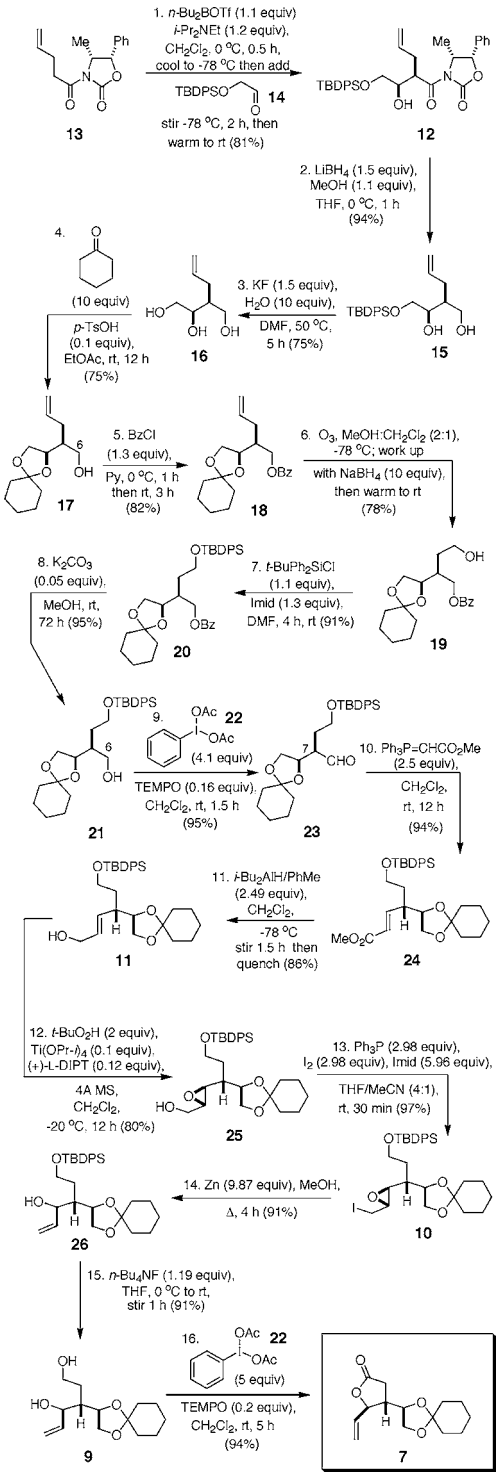
Following O-benzoylation of **17** with benzoyl chloride, the double bond of **18** was ozonolytically cleaved and the ozonides were reduced with $NaBH_4$; alcohol **19** was isolated in 78% overall yield. The latter was then O-silylated to obtain **20**, and its O-benzoate grouping was removed with K_2CO_3/MeOH (without causing *O*-silyl migration). The desired alcohol **21** was now in a format appropriate for further oxidation and Wittig homologation.

A range of methods were investigated for converting alcohol **21** into aldehyde **23**, including Swern oxidation ($COCl_2$/Me_2SO) which, rather surprisingly, caused catastrophic loss of the cyclohexylidene grouping. Most unusually, the catalytic TPAP/NMO oxidation[11] protocol also proved problematic, causing significant epimerization (ca. 10−15%) of the C(7) stereocenter, notwithstanding it performing efficiently in the chemical conversion of **21** into the aldehyde (95% yield). As a result, we evaluated alternative oxidants for accomplishing this transformation and, after much effort, eventually discovered that catalytic TEMPO and excess [bis(acetoxy)iodo]benzene (BAIB)[12] in CH_2Cl_2 could successfully produce the desired aldehyde **23** without any epimerization at C(7). Aldehyde **23** was thereafter condensed with carbomethoxymethylenetriphenylphosphorane in CH_2Cl_2 to give the (*E*)-enoate **24** as essentially a single geometrical isomer in 94% yield.

Compound **24** was readily reduced to **11** with DIBAL-H in PhMe/CH_2Cl_2 at −78 °C over a 1.5 h period. We found

(5) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Dall'Acqua, F.; Viola, G. *Tetrahedron* **2003**, *59*, 5215.
(6) (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755. (b) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. (c) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.
(7) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(8) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(9) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2001**, *3*, 3791.
(10) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2198.
(11) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(12) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

Scheme 2. Route Developed to Lactone **7**



it necessary to keep the temperature of this reduction at −78 °C throughout, otherwise unwanted cleavage of the primary TBDPS group began to occur, even at temperatures as low as −40 °C. However, by adhering to the −78 °C procedure that we have outlined (in the Supporting Information), excellent results (86% yield) were generally obtained.

With the desired allylic alcohol **11** in hand, we next investigated the Sharpless AE[7] needed to secure 2,3-epoxy alcohol **25**. Again, the latter was produced with high stereocontrol, as essentially a single diastereoisomer. It was immediately iodinated at room temperature with Ph_3P, I_2, and imidazole[13] in THF and MeCN. Significantly, the inclusion of MeCN proved critical to the success of this reaction, enabling the desired iodo-epoxide **10** to be formed efficiently in good yield (97%). Treatment of **10** with Zn dust in MeOH then effected the desired reductive elimination to provide the allylic alcohol **26** in 91% yield. O-Desilylation with *n*-Bu_4NF subsequently provided **9**.

Although the direct conversion of epoxy alcohol **25** into **26** was examined, using Yadav's titanocene chloride (Cp_2-TiCl/THF) reduction procedure,[14] sadly, we were unable to detect any of **26** in the reaction mixture.

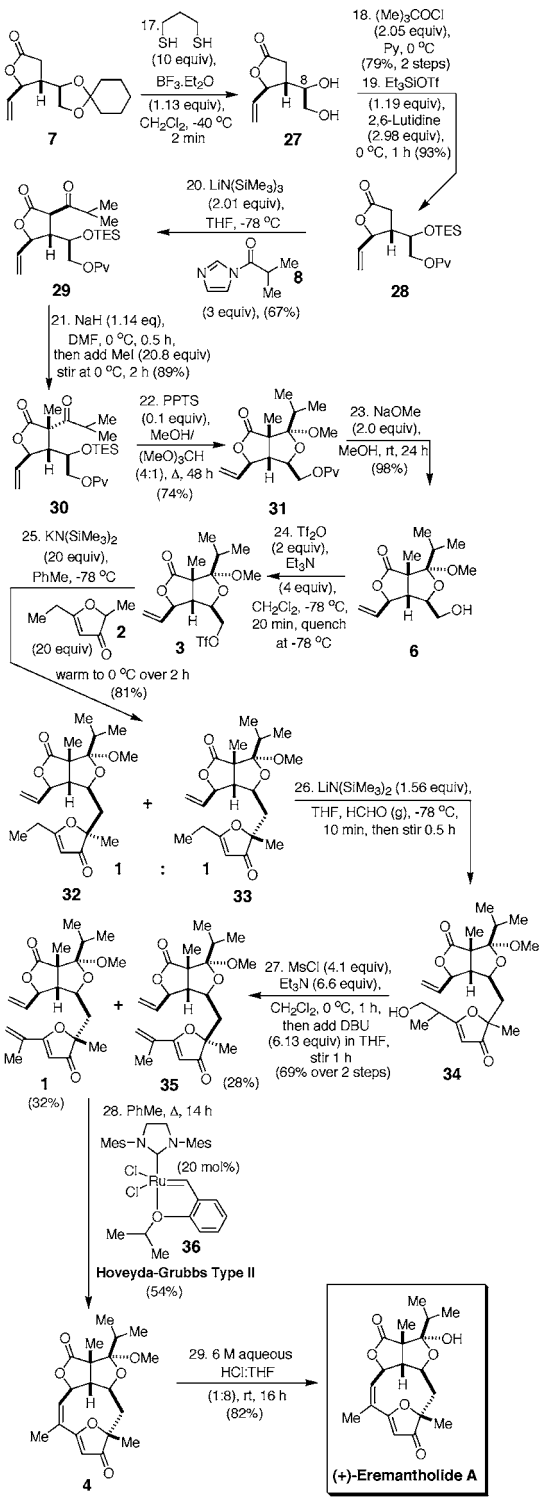
The time had now come for us to attempt the all-important chemoselective oxidation of **9** to the chiral butyrolactone **7**. After abortively screening a number of normally quite selective oxidants for generating γ-butyrolactones from 1,4-diols, including TPAP/NMO,[15] we eventually found that the catalytic TEMPO/BAIB oxidation system[12,16] could very cleanly deliver the desired lactone **7** in 94% yield. We were now in an excellent position to complete the synthesis of alcohol **6** (Scheme 3). Initially, we successfully C-acylated **7** with **8** and thereafter C-methylated the resulting β-keto ester with MeI (see Scheme 1) but observed that the subsequent Fischer glycosidation with MeOH/$(MeO)_3CH$/PPTS did not yield any of the desired methyl glycoside **6**. Instead, an internal acetal was formed involving the C(9) oxygen (for the precise structure of this undesired product, see structure **45** on pages 163−170 of our Supporting Information).

A decision was therefore made to remove the cyclohexylidene grouping from **7** with 1,3-propanedithiol and BF_3-Et_2O[10,17] (Scheme 3), and selective O-pivaloylation was subsequently attempted on the C(9) OH of diol **27**. Following O-silylation of the product monopivaloate with Et_3SiOTf, the desired C-acylation of **28** proceeded admirably using $LiN(SiMe_3)_2$ as the base and **8** as the electrophile. The enolate derived from **29** was thereafter reacted with MeI to give **30**. Exposure of **30** to PPTS/MeOH/$(MeO)_3CH$ now cleaved the TES group from O(8) and brought about the desired Fischer glycosidation at C(16) to give **31**. The Piv group was detached from **31** with NaOMe/MeOH, and alcohol **6** was converted into iodide **5** (see Scheme 1 for this structure) by successive O-mesylation and displacement with NaI/butanone at reflux. Unfortunately, iodide **5** proved unreactive toward all the metal enolates that we prepared from **2**. We therefore conducted all subsequent alkylation chemistry with the *O*-triflate **3**, analogously to Tadano et al.[2b]

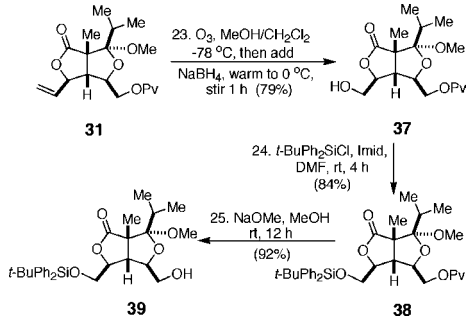
Initially, we used a "chiral" lithium enolate generated from **2** with lithium bis[(*S*)-α-methylbenzylamide][6] in PhMe at

(13) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
(14) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *Chem. Commun.* **1990**, 843.
(15) Shi, H.; Liu, H.; Bloch, R.; Mandville, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1423.
(16) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.
(17) **Important Note**: Under these conditions, we find that **27** is always formed alongside approximately 14−17% of a lactone migration product that is difficult to remove at this stage; the latter impurity arises from attack of the C(8)-OH in **27** on its own lactone carbonyl.

Scheme 3. Final Stages of Our Total Synthesis of (+)-Eremantholide A



Scheme 4. Intersection with Tadano's Alcohol **39**



behavior, we conducted the union of **2** and **3** under "achiral" enolization conditions. The best result came when KHMDS was used as the base in PhMe; it produced a 1:1 mixture of **32**/**33**. However, instead of separating the two individual isomers at this stage, we generally found it more convenient to deprotonate the mixture of **32** and **33** at C(4) and trap the resulting dienolates with gaseous formaldehyde to obtain **34** as a mixture of diastereomers. Exposure of **34** to MsCl/Et_3N, followed by DBU, very cleanly induced elimination of the intermediary *O*-mesylate esters to give **1** and **35** in 69% yield; the two trienes were separated by chromatography. Intriguingly, triene **1** cyclized in respectable yield (54%) to **4**[2b] when subjected to RCM with the Hoveyda−Grubbs catalyst **36**,[18] whereas compound **35** showed no tendency to cyclize; instead, it preferentially cross-metathesized.

The final step of our total synthesis was the acid-induced hydrolysis of known[2b] methyl glycoside **4** under the conditions previously reported by Tadano et al.;[2b] the end result was (+)-eremantholide A, formed in 82% yield.

In furtherance of our work, we also successfully converted lactone **31** into Tadano's advanced intermediate **39**[2b] for (+)-eremantholide A by the three-step sequence shown in Scheme 4; this now shortens the route needed to access Tadano's AB-alcohol[2b] by eight steps and provides **39** by a pathway that is 26 steps overall from a commercially available chiral auxiliary. Our new pathway to **39** thus constitutes a formal total synthesis of (+)-eremantholide A.

Future work in our laboratory will attempt to use our new route to construct novel eremantholide analogues and photoaffinity labeled probes to help us elucidate the mechanism(s) of antitumor action of (+)-eremantholide A.[4]

Acknowledgment. We thank the EPSRC (GR/S81582/01) for generous financial support of this program.

Supporting Information Available: Full experimental procedures and detailed spectral data of all key compounds are reported. Copies of 500 MHz ^1H and 125 MHz ^{13}C NMR spectra are provided along with IR spectra and HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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low temperature (−78 to 0 °C) to effect the diastereoselective alkylation of **3** and observed that a 2.48:1 mixture of **32**/**33** was formed, in which the undesired isomer **32** predominated. Somewhat surprisingly, a similar ratio of products (2.33:1 of **32**/**33**) was formed when lithium bis[(*R*)-1-α-methylbenzylamide][6] was used for the kinetic deprotonation of **2** in PhMe (see Supporting Information)! In light of this unusual

(18) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) For the successful use of **36** to construct the highly strained ring system of ingenol, see: Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.