HETEROCYCLES, Vol. 78, No. 4, 2009, pp. 873 - 889 . © The Japan Institute of Heterocyclic Chemistry
Received, 6th October, 2008, Accepted, 4th November, 2008, Published online, 7th November, 2008
DOI: 10.3987/REV-08-647

RECENT ADVANCES IN THE TOTAL SYNTHESIS OF XANTHANOLIDE SESQUITERPENOIDS

Kozo Shishido*

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

E-mail: shishido@ph.tokushima-u.ac.jp

Abstract – Recent advances in the total synthesis of xanthanolide/dinorxanthanolide sesquiterpenoids are described. This family of natural products can be divided into two structural classes according to the stereochemistry at C8 of the basic carbon framework, the oxabicyclo[5.3.0]decene core, i.e., the *cis*- and *trans*-fused γ-butyrolactone series. This article reviews the successful total syntheses of the five natural products, 8-*epi*-xanthatin (**1**) and sundiversifolide (**2**) (the *cis*-series), and 11α,13-dihydroxanthatin (**3**), xanthatin (**4**) and diversifolide (**5**) (the *trans*-series).

Xanthanolide sesquiterpenoids[1] are a class of natural products isolated primarily from the genus *Xanthium* (Compositae). They possess a characteristic oxabicyclo[5.3.0]decene core as their common basic carbon framework and exhibit a wide variety of biological activities, *e.g.* *anti*-tumor,[2] *anti*-malarial[3] and *anti*-bacterial, particularly against MRSA.[4] Two other dinorxanthane sesquiterpene lactones, sundiversifolide (**2**)[5] and diversifolide (**5**),[6] have also been isolated, sundiversifolide from the sunflower (*Helianthus annuus* L., Asteraceae) and diversifolide from the perennial herb (*Tithonia T. diversifolia* (Hernsl.) A. Gray, Comositae), respectively. Sundiversifolide (**2**), which has been found to contain a plant growth-inhibiting substance (allelochemical), potentially could become a lead for the development of environmentally benign herbicides. Structurally, the xanthanolide and dinorxanthanolide sesquiterpenoids can be divided into either the *cis*- or the *trans*-fused γ-butyrolactone series, depending on the stereochemistry at C8. Not surprisingly, the promising biological profiles and intriguing chemical

structures of these compounds have stimulated intense interest in these natural products resulting in numerous synthetic studies being directed towards their total synthesis over the past several years. In this review, we focus on the recent advances in the successful total syntheses of five kinds of xanthanolide and dinorxanthanolide sesquiterpenoids: 8-*epi*-xanthatin (**1**) and sundiversifolide (**2**) (the *cis*-series), and 11α,13-dihydroxanthatin (**3**), xanthatin (**4**) and diversifolide (**5**) (the *trans*-series). (**Figure 1**)

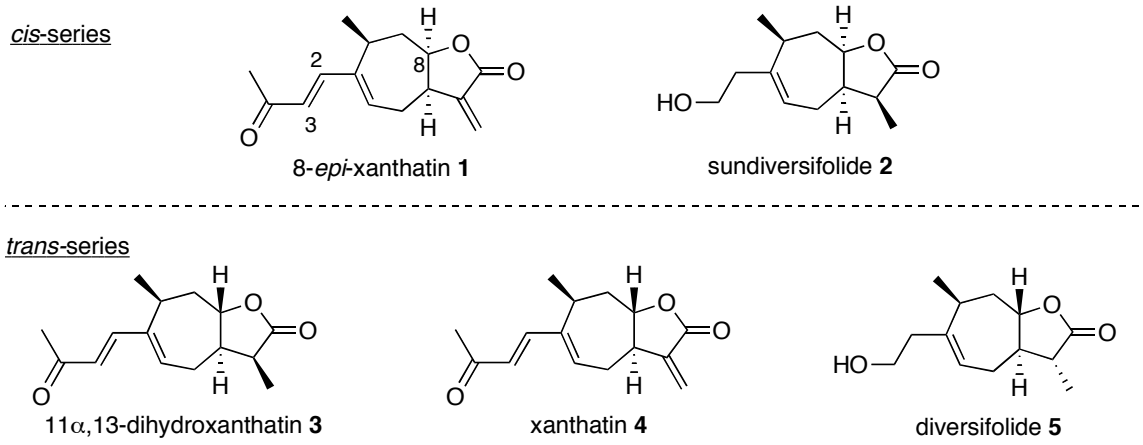
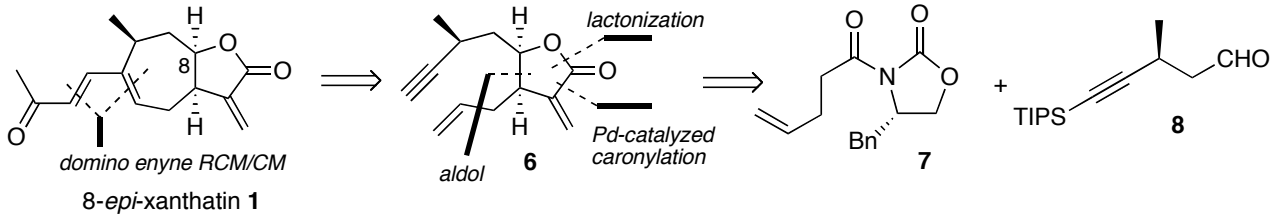


Figure 1. Xanthanolide sesquiterpene lactones

Total synthesis of (+)-8-epi-xanthatin[9]

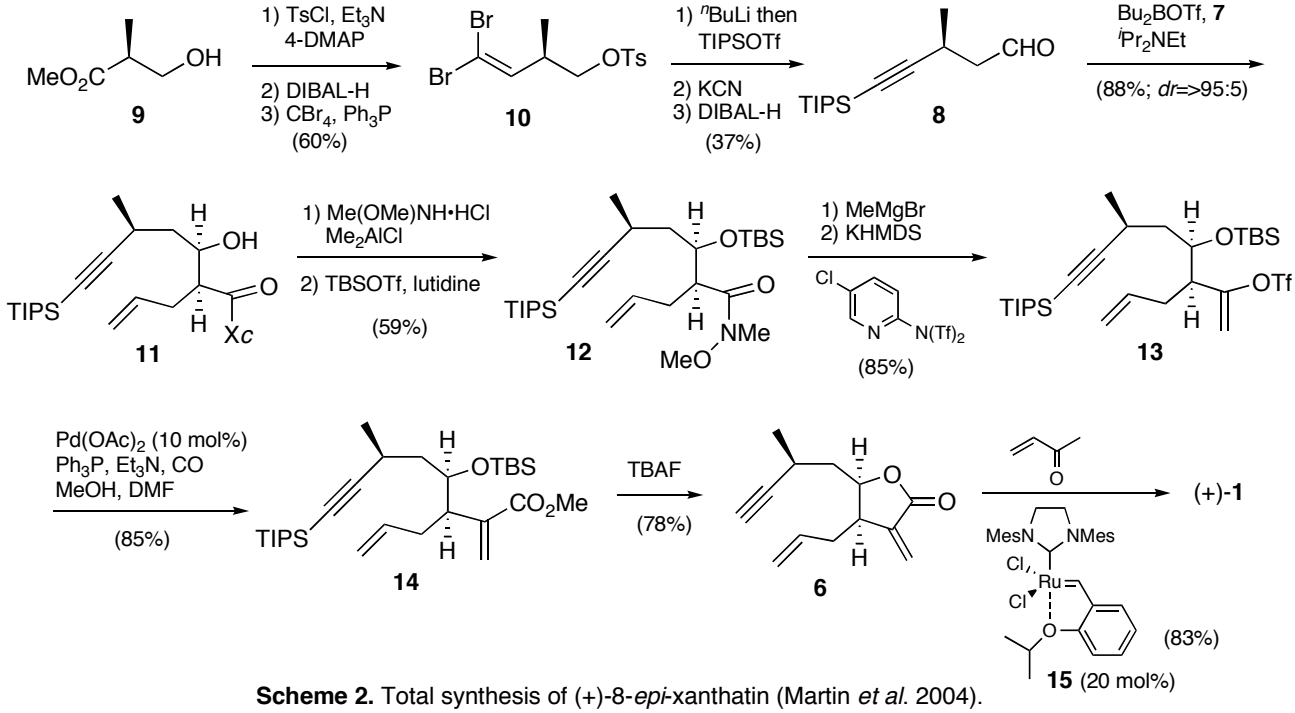
8-*epi*-Xanthatin (**1**), commonly isolated from the extracts of the aerial parts of various species in the genus *Xanthium*,[7] has also been obtained upon elimination of acetic acid from xanthumin (8-*epi*-2-acetoxy-3-hydroxanthatin).[8] It has been shown to inhibit larval growth of Drosophila melanogaster (fruit fly)[7c] and the *in vivo* proliferation of several cultured human tumor cell lines.[2] Not only does it display anti-malarial activity,[3] but it was also found to inhibit the farnesylation process of human lamin-B by farnesyltransferase in a dose-dependent manner *in vitro*.[2b] A representative of the *cis*-fused γ-lactone series possessing a characteristic (*E*)-conjugated dienone functionality, this natural product was synthesized in 2005, by Marin *et al.* in the first reported total synthesis of **1**.[9] Its key features are 1) a sequence for palladium-catalyzed carbonylation of an enol triflate[10] and lactonization to construct the α-methylene-γ-butyrolactone functionality, and 2) a fascinating domino enyne ring closing metathesis (RCM)/cross metathesis (CM)[11] process to elaborate the seven-membered carbocycle with its pendant enone array (**6** → **1**). The lactone **6** with the requisite stereochemistry would be prepared *via* an asymmetric aldol coupling of **7** with the aldehyde **8**. (Scheme 1) The synthesis of the *trans*-fused xanthanolide, 11α,13-dihydroxanthatin **3**, was also reported at approximately the same time by the group

of Morken [12] employing a similar key strategy, *i.e.*, enyne RCM[13] followed by CM,[14] for the construction of the seven-membered ring and the conjugated dienone moiety.



Scheme 1. Strategic bond disconnections and retrosynthetic analysis of (+)-8-*epi*-xanthatin

The total synthesis of the 8-*epi*-xanthatin (**1**) is shown in Scheme 2. The enantiomerically pure **9** was converted *via* the dibromoalkene **10** to the acetylenic aldehyde **8** which was treated with **7** to give the aldol adduct **11** with high diastereoselectivity. The enyne **14** with the requisite stereochemistry was prepared by palladium-catalyzed carbomethoxylation[10] of the enol triflate **13**, formed using the Comins triflimide[15] *via* the Weinreb amide **12**.[16] Desilylation of **14** with TBAF led to the spontaneous formation of the α-methylene-γ-butyrolactone **6**. Finally, the pivotal domino enyne RCM/CM reaction[11] of **6** in the presence of methyl vinyl ketone and the Grubbs-Hoveyda catalyst **15**[17] was realized to give (+)-**1** in 83% yield. The total synthesis was completed efficiently by a route that required only 14 steps in the longest linear sequence and proceeded in an overall yield of 5.5%. (Scheme 2)

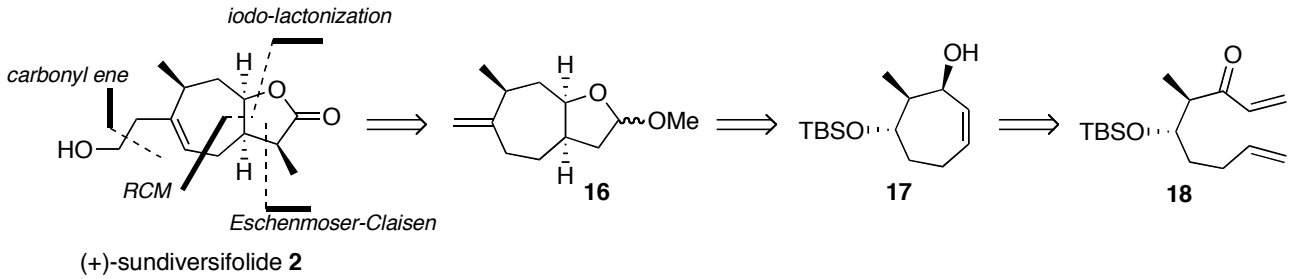


Scheme 2. Total synthesis of (+)-8-*epi*-xanthatin (Martin *et al.* 2004).

First total synthesis of (+)-sundiversifolide[18]

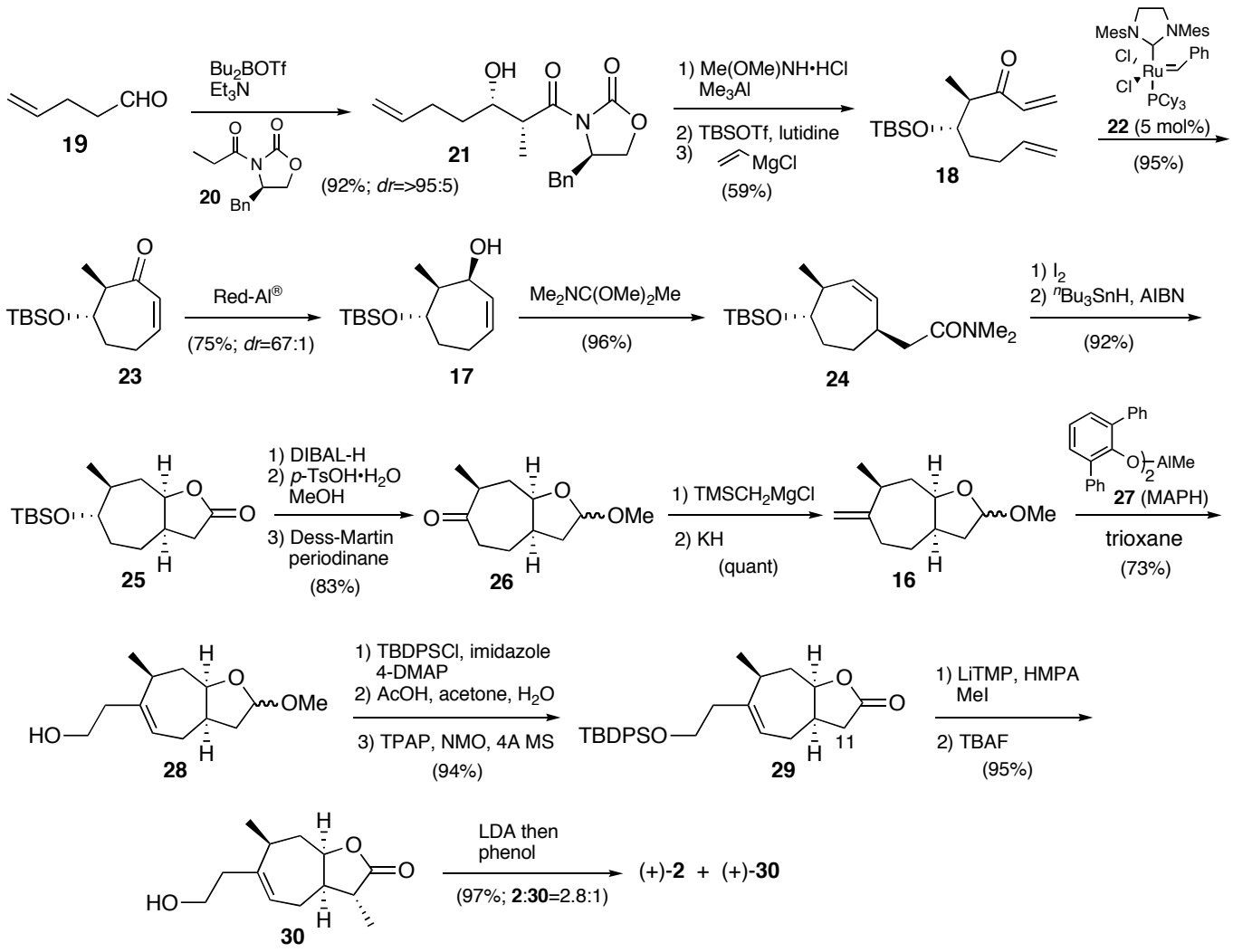
Sundiversifolide (**2**) was isolated from the exudates of *Helianthus annuus* L., germinating sunflower seeds.[5] This compound inhibited shoot and root growth of cat's-eye by about 50% at a concentration of 30 ppm and also showed species-selective activity in the shoot and root growth of various tested plants, *e.g.* tomato, crabgrass and barnyard grass. Although sundiversifolide has been recognized as having an allelopathic function in sunflowers, interestingly, it did not inhibit shoot growth of the sunflower itself.

The first total synthesis was accomplished by our group in 2007,[18] the key features of which include (i) the use of sequential RCM[14] and diastereoselective reduction (**18** → **17**), (ii) the Eschenmoser-Claisen rearrangement[19] followed by iodolactonization, reduction and acetalization (**17** → **16**) to install the *cis*-fused oxabicyclo[5.3.0]decene core, and (iii) the use of the Maruoka-Yamamoto methylaluminum bis(2,6-diphenylphenoxide) (MAPH)-mediated carbonyl ene-reaction[20] of **16** to construct the olefinic ethanol functionality. (Scheme 3)



Scheme 3. Strategic bond disconnections and retrosynthetic analysis of (+)-sundiversifolide

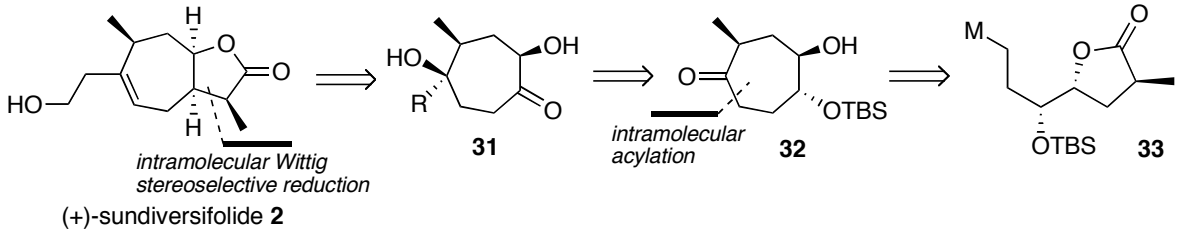
The RCM of the optically pure diene **18**, which was prepared starting from an asymmetric aldol reaction of **19** and **20**, using the second-generation Grubbs catalyst **22**, provided efficiently the seven-membered enone **23**. Reduction with Red-Al® produced the alcohol **17** with the (*R*)-configuration in a highly diastereoselective fashion. The Eschenmoser-Claisen rearrangement resulted in the formation of **24** as a single product. Construction of the bicyclic core with the olefinic ethanol appendage was achieved by a sequential iodolactonization, Peterson olefination,[21] and the MAPH-mediated carbonyl ene-reaction to give **28** in good overall yield. Installation of the β-methyl group at C11 of **29** was realized via successive α-selective methylation and epimerization by kinetic protonation to give a 2.8:1 separable mixture of sundiversifolide **2** and the epimer **30**. Thus the first total synthesis of the natural enantiomer (+)-**2** was completed in an overall yield of 13.3% (21 steps from **19**). (Scheme 2)



Scheme 4. Total synthesis of (+)-sundiversifolide (Shishido *et al.* 2007).

Second total synthesis of (+)- and (–)-sundiversifolide[22]

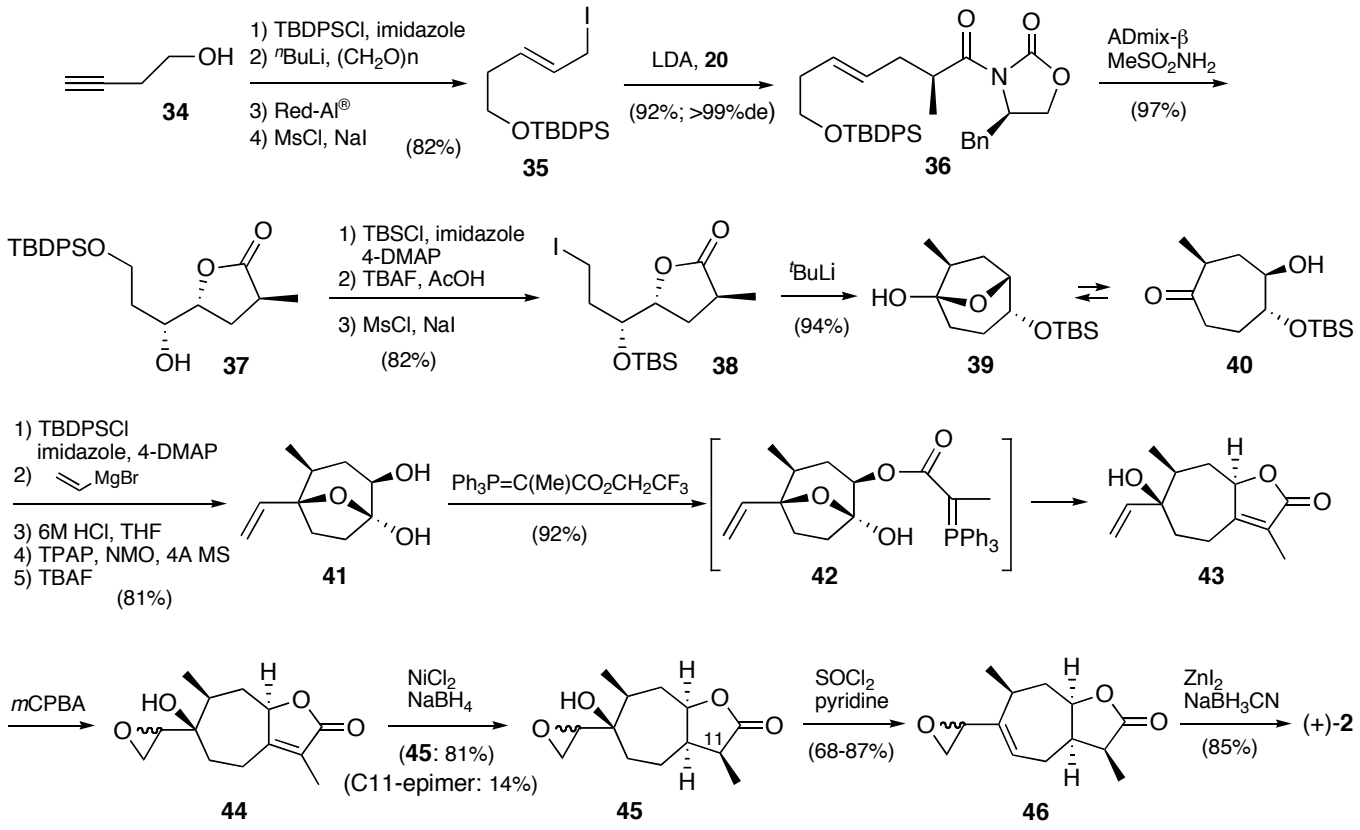
Another synthesis of sundiversifolide has been described by Shindo *et al.*[22] Among its interesting aspects should be noted 1) the intramolecular acylation[23] of the organolithium species **33** for the elaboration of the functionalized cycloheptanone **32** and a sequential intramolecular Wittig reaction of **31**, and 2) the diastereoselective reduction of the resulting butenolide for the construction of the *cis*-fused α-methyl-γ-lactone moiety with the requisite stereochemistry in **2**. (Scheme 5)



Scheme 5. Strategic bond disconnections and retrosynthetic analysis of (+)-sundiversifolide

The synthesis began with the conversion of 3-butyn-1-ol **34** to the iodide **35**, which was subjected to asymmetric alkylation with **20** to give **36** with high diastereoselectivity. Asymmetric dihydroxylation

using ADmix-β produced the hydroxy lactone **37** efficiently. A pivotal cyclization of the iodo lactone **38** using *t*BuLi provided an equilibrium mixture of **39** and **40**,[24] which was converted to the hydroxy hemiacetal **41** by a five-step sequence of reactions. Treatment of **41** with the Wittig reagent (Ph_3P=C(Me)$CO_2CH_2CF_3$) provided the butenolide **43** presumably *via* transesterification giving the intermediate **42** followed by intramolecular Wittig olefination. The structure of **43** was unambiguously established by X-ray crystallographic analysis. After epoxidation, the epoxide **44** was treated with nickel boride (generated *in situ* from $NiCl_2$ and $NaBH_4$)[25] to give the bicyclic *cis*-lactone **45** (81%) along with the C11-epimer (14%). Dehydration followed by regioselective cleavage of the epoxide in **46** with ZnI_2 and $NaBH_3CN$[26] provided (+)-sundiversifolide **2**. (Scheme 6) The total synthesis was completed efficiently in 25% overall yield. In addition, the unnatural enantiomer (–)-**2** was also synthesized in a similar manner, using the chiral oxazolidinone *ent*-**20** derived from L-Phe in the asymmetric alkylation and ADmix-α in the asymmetric dihydroxylation. It should be emphasized that the absolute structure of the natural sundiversifolide was established by this work, i.e., HPLC analysis using a chiral column indicated that the natural **2** was identical with the synthetic (+)-**2**.

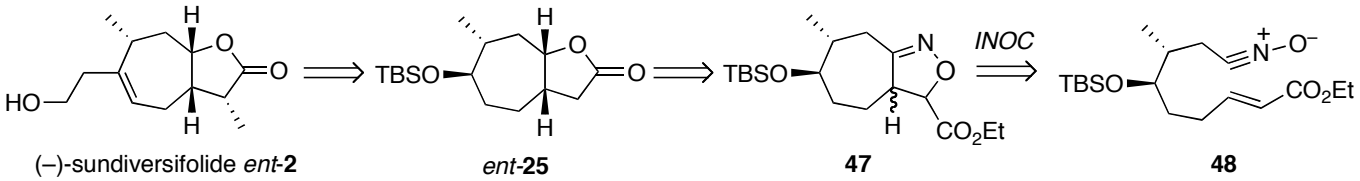


Scheme 6. Total synthesis of (+)-sundiversifolide (Shindo *et al.* 2008).

Third total synthesis of (–)-sundiversifolide[31]

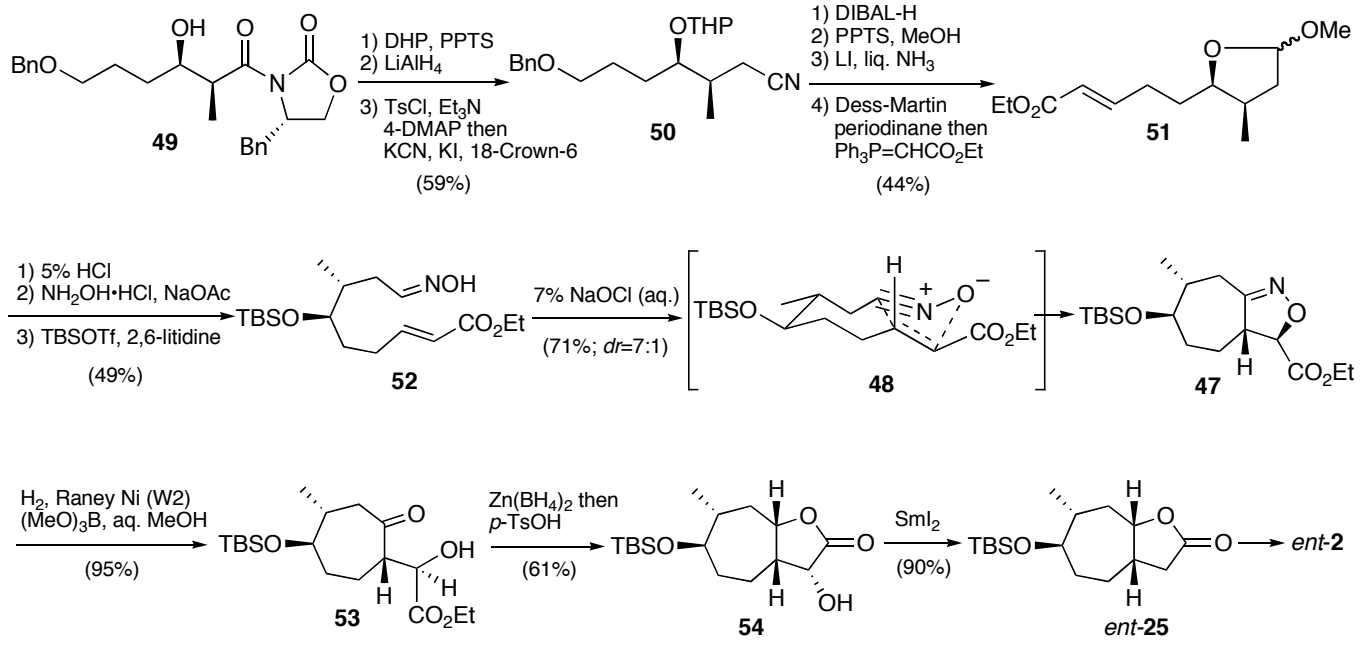
In the course of our program directed toward the search for promising lead compounds for the development of new allelochemicals and antibacterial drugs, we decided to undertake the synthesis of the unnatural enantiomer of sundiversifolide (–)-**2** employing a new strategy for the construction of the key

intermediate **25** in the synthesis of (+)-**2**. From a retrosynthetic perspective, (–)-**2** would be derived from the bicyclic lactone *ent*-**25** *via* the procedure we developed in the synthesis of the natural enantiomer (+)-**2** (Scheme 4). For the synthesis of (–)-**25**, the diastereoselective 1,3-dipolar [3+2] cycloaddition reaction[27] of the nitrile oxide (**48** → **47**) was used as the key reaction step.



Scheme 7. Retrosynthetic analysis of (–)-sundiversifolide

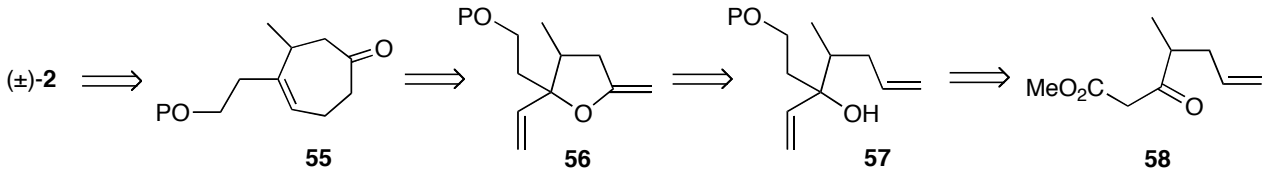
The known aldol product **49** was converted to compound **52** possessing the oxime and the conjugate ester moieties *via* **50** and **51**. Treatment of **52** with a 7% aqueous solution of NaOCl in CH_2Cl_2 provided the isoxazoline **47** as the major product (*dr*=7:1). The diastereoselectivity can be explained by postulating that the transition state has the conformation shown in **48**.[28] After reductive hydrolysis, the resulting keto alcohol **53** was sequentially treated with $Zn(BH_4)_2$[29] and *p*-TsOH to give the α-hydroxy-γ-butyrolactone **54**, which was exposed to SmI_2[30] providing the requisite *ent*-**25**. According to the protocol for the synthesis of (+)-**2**, *ent*-**25** was converted to *ent*-**2**. (Scheme 6)[31]



Scheme 8. Total synthesis of (–)-sundiversifolide (Shishido *et al.* 2008).

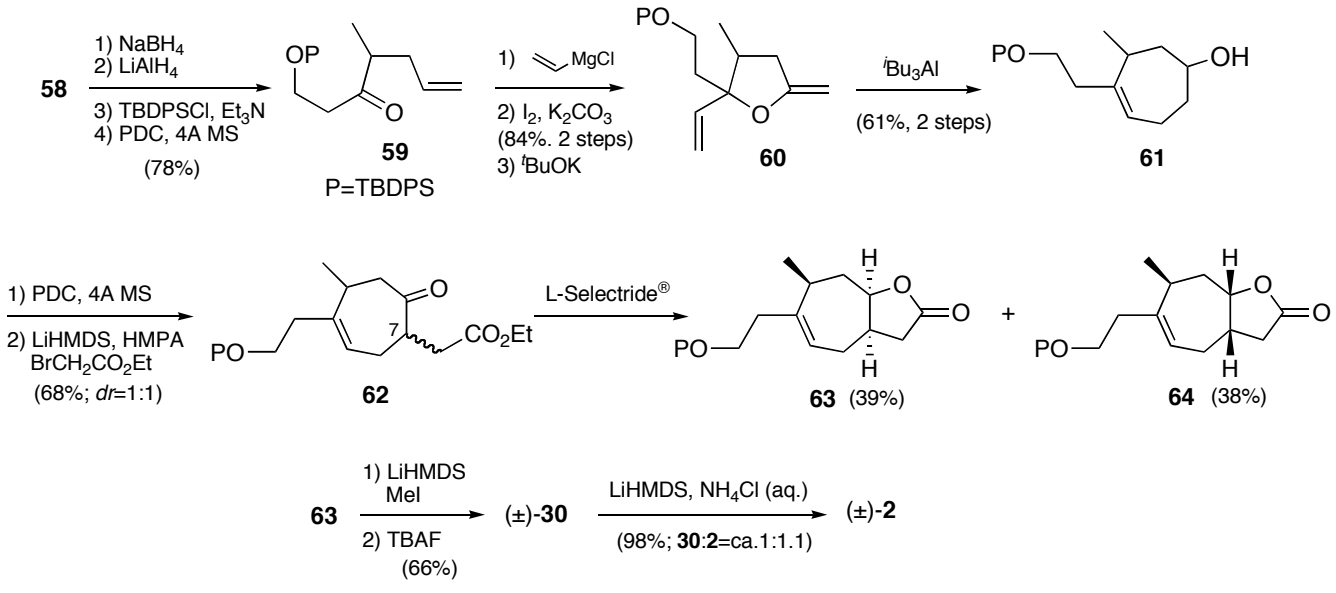
Total synthesis of (±)-sundiversifolide[32]

A concise synthesis of racemic sundiversifolide was reported by Takikawa *et al.*[32] The retrosynthetic analysis is shown in Scheme 9. The key step of the synthesis is a Lewis acid-mediated Claisen rearrangement[33] (**56** → **55**) for the construction of the cycloheptenone core, with substrate **56** being prepared from the known keto ester **58** *via* an iodoetherification of the dienyl alcohol **57**. (Scheme 9)



Scheme 9. Retrosynthetic analysis of (±)-sundiversifolide

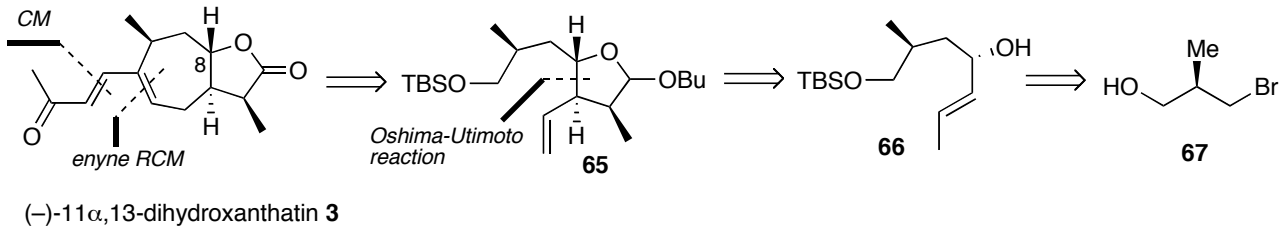
The keto ester **58** was converted in four steps into **59** and sequential vinylation, iodoetherification and β-elimination provided the cyclic allyl vinyl ether **60**. Treatment of **60** with triisobutylaluminium (TIBAL) in toluene[34] (necessary to promote higher yields) resulted in the formation of the cycloheptenol **61** (51% yield from **59**) through Claisen rearrangement and reduction of the resulting ketone **55**. The kinetically controlled regioselective introduction of the acetate unit at C7 (sundiversifolide numbering) was realized to give a 1:1 diastereomeric mixture of the keto esters **62** in 68% yield. Reduction with L-Selectride® produced a diastereomeric mixture of the *cis*-lactones **63** and **64** in 39% and 38% yield, respectively. Methylation followed by desilylation provided (±)-**30**, which was exposed to kinetic protonation conditions to give a separable 1.1:1 mixture of (±)-**2** and (±)-**30** in good yield. The overall yield of (±)-**2** was 3.5% (14 steps from **58**). (Scheme 10)



Scheme 10. Total synthesis of (±)-sundiversifolide (Takikawa *et al.* 2007).

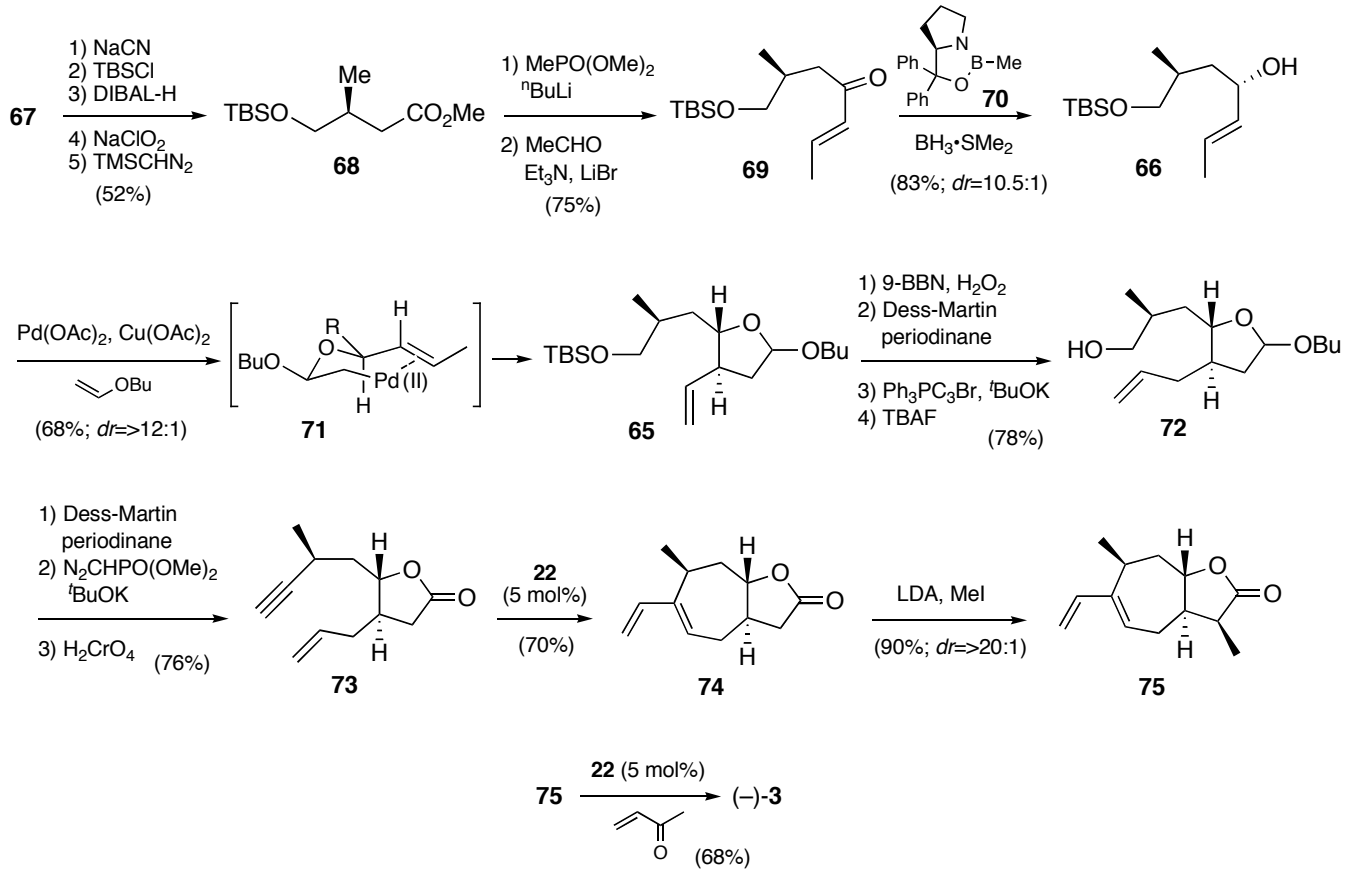
Total synthesis of (–)-11α,13-dihydroxanthatin[12]

11α,13-Dihydroxanthatin **3** was isolated from *Xanthium strumarium* as a representative of the trans-fused xanthanolide sesquiterpene lactones.[35] The chemical structure of **3** contains a β-oriented methyl group instead of the exocyclic methylene unit present in xanthatin **4**, at the α position of the γ-butyrolactone ring. Although the biological profile of **3** has never been reported, a comparison of the antifungal activity of xanthatin **4** with that of dihydroxanthatin **3**, which lacks any antifungal activity at a dose of 250 μg, clearly indicates that the α-methylene-γ-butyrolactone functionality is essential for the biological activity.[36] In 2005, for the first time, an asymmetric total synthesis of 11α,13-dihydroxanthatin **3** was completed by Morken *et al.*[12] and includes as key features 1) the use of a sequential enyne RCM and CM[14c] for the construction of the seven-membered carbocycle with the dienone functionality and 2) an application of the stereoselective Oshima-Utimoto reaction[37] to elaborate the *trans*-fused butyrolactone moiety (**66** → **65**). (Scheme 11)



Scheme 11. Strategic bond disconnections and retrosynthetic analysis of (–)-11α,13-dihydroxanthatin

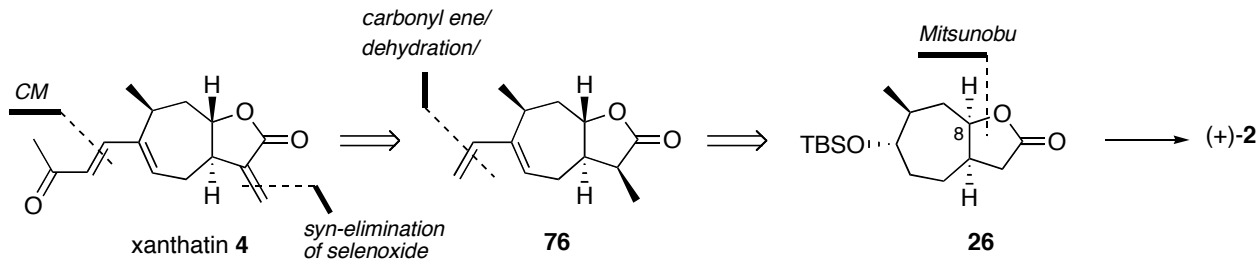
The commercially available bromoalcohol **67** was converted *via* a seven-step sequence to the chiral enone **69**, which was reduced to **66** using the *R*-enantiomer of the Itsuno-Corey oxazaborolidine **70**.[38] The allyl alcohol **66** was subjected to the catalytic Oshima-Utimoto reaction, namely, treatment with butyl vinyl ether and $Cu(OAc)_2$ in the presence of 10 mol% of $Pd(OAc)_2$ to give **65**, *via* transition state **71**, in 68% yield with >12:1 diastereoselectivity. After homologation followed by deprotection, the resulting **72** was oxidized with Dess-Marin periodinane, treated with the Gilbert-Seyferth reagent[39] and oxidized with chromic acid to give the enyne lactone **73**. Treatment of **73** with the Grubbs catalyst **22** provided the bicyclic diene **74**. Methylation with LDA and MeI gave the β-methylated lactone **75** diastereoselectively (*dr*=>20:1).[40] Finally, the CM of **75** with methyl vinyl ketone using the same catalyst **22** as in the case of the enyne RCM provided (–)-11α,13-dihydroxanthanolide **3** in an overall yield of 5.6% (19 steps from **67**). (Scheme 12)



Scheme 12. Total synthesis of (–)-11α,13-dihydroxanthatin (Morken *et al.* 2004).

Total synthesis of (–)-xanthatin[45]

Xanthatin **4** was first isolated from *Xanthium pennsylvanicum* by Little *et al.* in their examination of the cocklebur for its antibacterial properties.[41] Its structure was established by Geissman *et al.*[42] who suggested that **4** would be derived from xanthinin (2-acetoxy-3-hydroxanthatin) during isolation, particularly on column chromatography.[42a] Xanthatin has also been isolated from *X. strumarium*,[42] *X. sibiricum*,[4] and *X. macrocarpum*,[43] and exhibits potent antibacterial activity against the *Staphylococcus aureus* species, including MRSA.[4] It was recently reported that xanthatin suppressed the expression of iNOS and COX-2 and the activity of NF-κB through the inhibition of LPS-induced I-κB-α degradation in microglia.[44] The first total synthesis was accomplished in 2008 by our group based on the strategy outlined in Scheme 13.[45] As the key intermediate for the total synthesis, the bicyclic dienyl lactone **76**, a penultimate intermediate in Morken's total synthesis of **3**,[12] was selected. It was thought that the exocyclic methylene could be installed via a *syn*-elimination of a selenoxide by taking into account the stereochemical nature of **76** for the diastereoselective introduction of the electrophile from the β-face of the lactone enolate; the total synthesis would be completed by CM of **76** with methyl vinyl ketone. The intermediate **76** would be prepared *via* the Mitsunobu inversion at C8 of the *cis*-fused lactone **26**, which is a key intermediate in our total synthesis of sudiversifolide.[18] (Scheme 13)

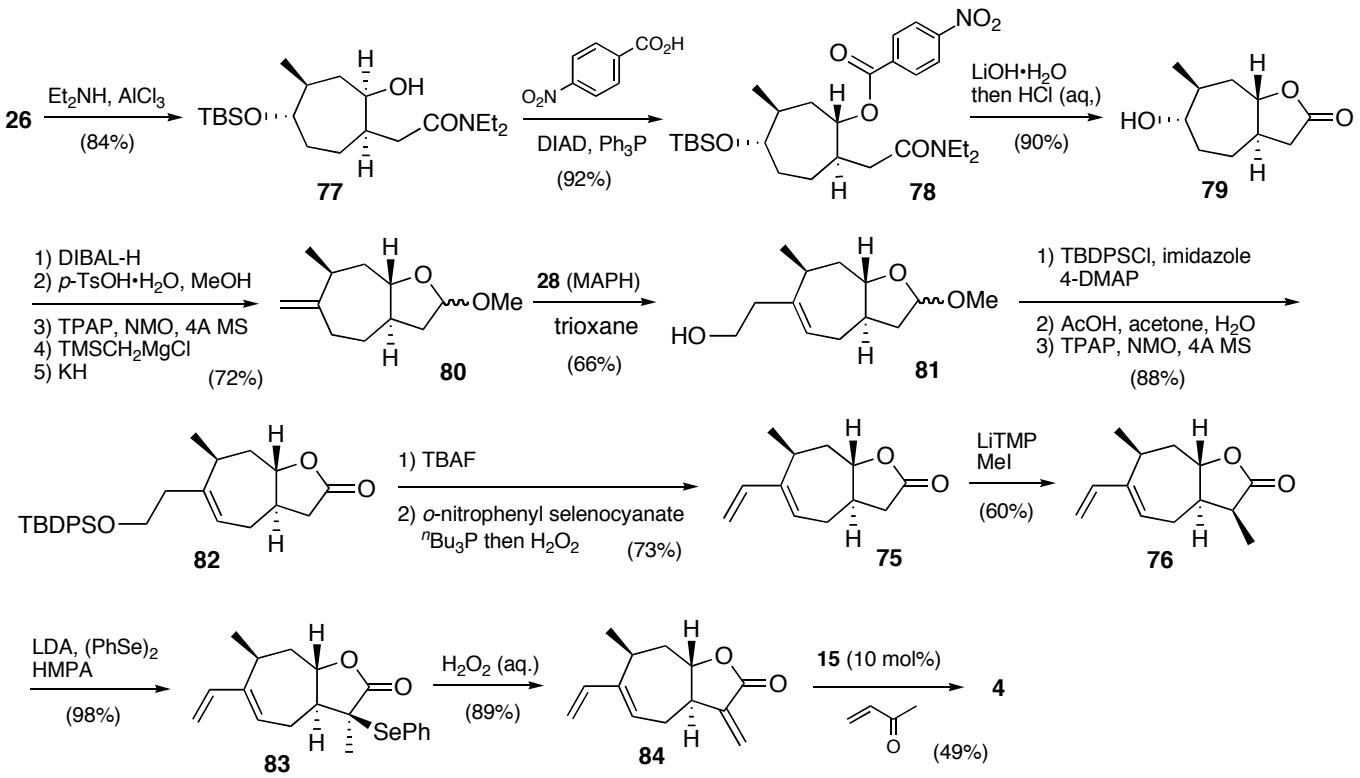


Scheme 13. Strategic bond disconnections and retrosynthetic analysis of (–)-xanthatin

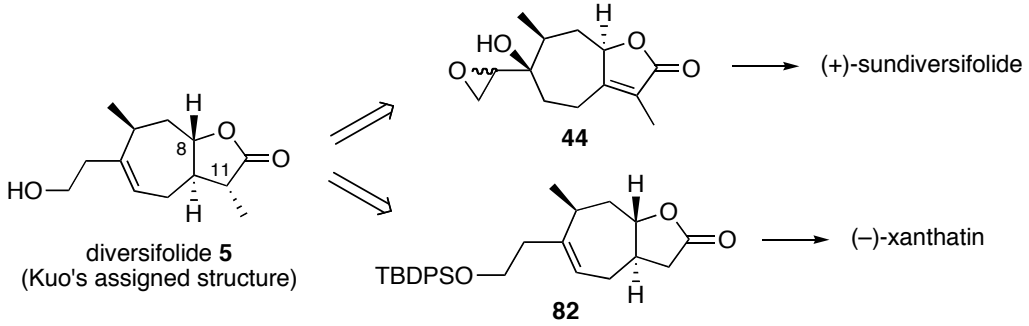
The lactone ring opening of **26** was achieved by treatment with Et_2NH and $AlCl_3$[46] to give the amide alcohol **77**, which was exposed to the Mitsunobu reaction using *p*-nitrobenzoic acid,[47] diisopropyl azodicarboxylate and Ph_3P to provide the benzoate **78** with inversion of configuration at the future C8. After hydrolysis and acidification, the resulting *trans*-fused lactone **79** was converted in five steps to **80**. This compound was then subjected to the MAPH-catalyzed carbonyl ene-reaction followed by regeneration of the lactone ring to furnish **82**. Desilylation and subsequent dehydration of the primary alcohol moiety by the Nishizawa-Grieco protocol[48] provided the diene **75**, which was methylated to give **76** as a single diastereoisomer. The spectral properties of **75** and **76** were identical with those reported by Morken indicating that an alternative synthesis of 11α,13-dihydroxanthatin has been formally accomplished at this stage. Phenylselenylation[49] of **76** provided diastereoselectively the selenide **83**, with the β-oriented phenylselenyl function, which was oxidized with H_2O_2 leading to the spontaneous formation of the α-methylene lactone **84** in good yield. Final CM was achieved using the Grubbs-Hoveyda catalyst **15**[17] to complete the total synthesis of (–)-xanthatin **4**. The overall yield was 5.4% (18 steps from **26**). (Scheme 14)

Total synthesis and structural revision of (–)-diversifolide[50]

Diversifolide **5** was isolated from the perennial herb *Tithonia T. diversifolia* (Hernsl.) A. Gray (Comositae) by Kuo *et al.* in 1999.[6] Its aerial parts have been used as a traditional treatment for hepatitis and hepatoma. Although a biological profile of diversifolide itself has never been reported, the compound was nonetheless expected to possess some biological activity. Kuo, in his report, did not establish the absolute configuration of **5** but, on spectroscopic analysis, assigned the structure to be a *trans*-fused dinorxanthanolide sesquiterpenoid. Because of the structural similarity of sundiversifolide and its potential biological activities, the Shindo and Shishido groups directed their efforts towards the total synthesis of **5**,[50] starting from the key intermediates **44**[22] and **82**,[45] in the syntheses of sundiversifolide **2** and xanthatin **4**, respectively, as shown in Scheme 15.



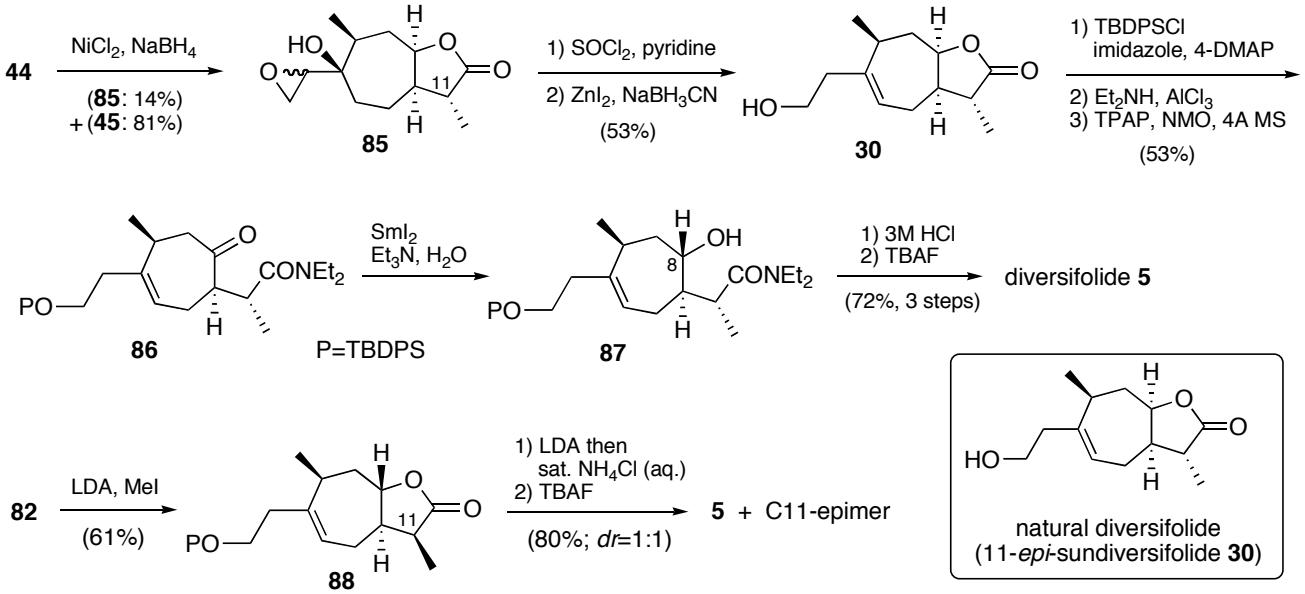
Scheme 14. Total synthesis of xanthatin (Shishido *et al.* 2008).



Scheme 15. Retrosynthetic analysis of (–)-diversifolide

As shown in the synthesis of sundiversifolide, when the bicyclic butenolide **44** was reduced with nickel boride, the two *cis*-lactones **45** and the C11-epimer **85** were obtained as a chromatographically separable mixture in 81% and 14% yield, respectively. The minor diastereomer **85** was converted *via* **30** (11-*epi*-sundiversifolide) to the ring-opened keto amide **86**, which was reduced with SmI_2 to give the alcohol **87** with the desired configuration at C8. After lactonization by acidic treatment and deprotection, diversifolide **5** was obtained. Alternatively, **5** was synthesized from the bicyclic *trans*-lactone **82**. Treatment of **82** with LDA and MeI provided the undesired C11-epimer **88** as the sole product. Attempted inversion at C11 using kinetic protonation conditions produced a separable 1:1 mixture of diastereoisomers, the desired isomer of which was desilylated to give **5**. However, the spectral data (^{1}H

and ^{13}C NMR) of **5** did not match those for the natural material reported by Kuo. Since the stereochemistry was confirmed by the NOE spectrum of **88**, Kuo's proposed stereochemistry has proven to be incorrect. After careful examination of the NMR spectra of the synthetic intermediates, we noticed that all the spectral data of the synthetic intermediate **30**, 11-*epi*-sundiversifolide (the C8-epimer of Kuo's assigned structure **5**), were identical with the reported values. Although there is a slight discrepancy in the chemical shift, we concluded that natural diversifolide is most likely the compound represented by **30**. The optical rotation allowed us to determine the absolute configuration of the diversifolide as shown in **30**. (Scheme 16)



Scheme 16. Total synthesis of Kuo's assigned structure of (–)-diversifolide (Shindo, Shishido *et al.* 2008).

CONCLUSION

In this article, we have described the successful total syntheses of the xanthanolide/dinorxanthanolide sesquiterpenoids, focusing on the five natural products of this family that have been reported since 2005. Because of their complex structural features and biological importance, the challenge to synthesize these interesting sesquiterpene lactones has tested the ingenuity of the synthetic community resulting in much interesting, important and novel chemistry. We think that even more valuable data will be forthcoming in the continuing, concerted efforts to synthesize the xanthanolide terpenoids.

ACKNOWLEDGEMENTS

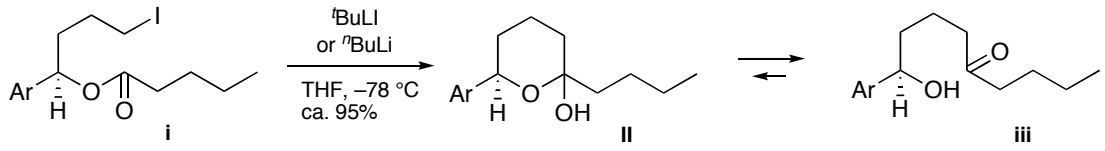
The work accomplished in our laboratories were supported financially by a Grant-in-Aid for Scientific Research (A) (No. 16209001) from the Japan Society for the Promotion of Science. The author thanks his graduate students, Hiromasa Yokoe and Makoto Kanematsu, for their help in preparing this manuscript.

REFERENCES

1. B. M. Fraga, *Nat. Prod. Rep.*, 1999, **16**, 711.
2. (a) J.–W. Ahn, Z. No, S.–Y. Ryu, O.–P. Zee, and S.–K. Kim, *Nat. Prod. Sci.*, 1995, **1**, 1; (b) Y. S. Kim, J. S. Kim, S.-H. Park, S.-U. Choi, C. O. Lee, S.-K. Kim, S. H. Kim, and S. Y. Ryu, *Planta Med.*, 2003, **69**, 375.
3. S. P. Joshi, S. R. Rojatkar, and B. A. Nagasampagi, *J. Med. Aromatic Plant Sci.*, 1997, **19**, 366.
4. Y. Sato, H. Oketani, T. Yamada, K. Shingyouchi, T. Ohtsubo, M. Kihara, H. Shibata, and. T. Higuti, *J. Pharm. Pharmacol.*, 1997, **49**, 1042.
5. S. Ohno, K. Tomita-Yokotani, S. Kosemura, M. Node, T. Suzuki, M. Amano, K. Yasui, T. Goto, S. Yamamura, and K. Hasegawa, *Phytochemistry*, 2001, **56**, 577.
6. Y.-H. Kuo and B.-Y. Lin, *Chem. Pharm. Bull.*, 1999, **47**, 428.
7. (a) N. M. Ghazy, A. A. Omar, E. M. Elrashidy, and A. M. Metwally, *Egypt. J. Pharm. Sci.*, 1988, **29**, 39; (b) C. McMillan, P. I. Chavez, and T. J. Mabry, *J. Biochem. Syst. Ecol.*, 1975, **3**, 137; (c) K. Kawazu, S. Nakajima, and M. Ariwa, *Experientia*, 1979, **35**, 1294; (d) F. Bohlmann, P. Singh, K. C. Joshi, and C. L. Singh, *Phytochemistry*, 1982, **21**, 1441; (e) A. A. Ahmed, J. Jakupovic, F. Bohlmann, H. A. Regaila, and A. M. Ahmed, *Phytochemistry*, 1990, **29**, 2211. 8-*epi*-Xanthatin (**1**) has also been isolated from de-etiolated sunflower (*Helianthus annuus*) seedlings as a plant growth-inhibiting substance, see: K. Yokotani-Tomita, J. Kato, S. Kosemura, S. Yamamura, M. Kushima, H. Kakuta, and K. Hasegawa, *Phytochemistry*, 1997, **46**, 503.
8. H. Minato and I. Horibe, *J. Chem. Soc.,* 1965, 7009.
9. (a) D. A. Kumar, J. B. Brenneman, and S. F. Martin, *Org. Lett.*, 2005, **7**, 4621; (b) D. A. Kumar, J. B. Brenneman, and S. F. Martin, *Tetrahedron*, 2006, **62**, 11437.
10. S. Cacchi, E. Morera, and G. Ortar, *Tetrahedron Lett.*, 1985, **26**, 1109.
11. (a) S. Randl, N. Lucas, S. J. Connon, and S. Blechert, *Adv. Syn. Catal.*, 2002, **344**, 631; (b) F. Royer, C. Vilain, L. Elkaim, and L. Grimaud, *Org. Lett.*, 2003, **5**, 2007; (c) H.-Y. Lee, H. Y. Kim, H. Tae, B. G. Kim, and J. Lee, *Org. Lett.*, 2003, **5**, 3439; (d) J. S. Clark, F. Elustondo, and M. C. Kimber, *Chem. Commun.*, 2004, 2470; (e) T. Kitamura, Y. Sato, and M. Mori, *Tetrahedron*, 2004, **60**, 9649; (f) S. S. Salim, R. K. Bellingham, and R. C. D. Brown, *Eur. J. Org. Chem.*, 2004, 800.
12. M. A. Evans and J. P. Morken, *Org. Lett.*, 2005, **7**, 3371.
13. For a review, see: S. T. Diver and A. J. Glessert, *Chem. Rev.*, 2004, **104**, 1317.
14. For reviews on methathesis, see: (a) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (b) A. Furstner, *Angew. Chem. Int. Ed.*, 2000, **39**, 3012; (c) S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.*, 2003, **42**, 1900; (d) R. H. Schrock and A. H. Hoveyda, *Angew. Chem. Int. Ed.*, 2003, **42**, 4592; (e) R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117; (f) Y. Schrodi and R. L. Pederson,

Aldrichimica Acta, 2007, **40**, 45; (g) A. H. Hoveyda and R. R. Zhugralin, *Nature*, 2007, **450**, 243.

15. D. L. Comins and A. Dehghani, *Tetrahedron Lett.*, 1992, **33**, 6299.
16. (a) A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **48**, 4171; (b) J. I. Levin, E. Turos, and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989; (c) D. A. Evans and W. C. Black, *J. Am. Chem. Soc.*, 1993, **115**, 4497.
17. S. B. Garber, J. S. Kingsbury, B. L. Gray, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.
18. H. Yokoe, H. Sasaki, T. Yoshimura, M. Shindo, M. Yoshida, and K. Shishido, *Org. Lett.*, 2007, **9**, 969.
19. (a) A. Eschenmoser, A. E. Wick, S. Felix, and K. Steen, *Helv. Chim. Acta*, 1964, **47**, 2425; (b) J. Mulzer, A. Galkina, and M. W. Gilbert, *Synlett*, 2004, **14**, 2558.
20. K. Maruoka, A. B. Concepcion, N. Murase, M. Oishi, N. Hirayama, and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 3943.
21. (a) D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780; (b) A. Vazquez and R. M. Williams, *J. Org. Chem.*, 2000, **65**, 7865.
22. K. Ohtsuki, K. Matsuo, T. Yoshikawa, C. Moriya, K. Tomita-Yokotani, K. Shishido, and M. Shindo, *Org. Lett.*, 2008, **10**, 1247.
23. A relevant protocol using SmI_2 has been reported, see: (a) G. A. Molander, *Acc. Chem. Res.*, 1998, **31**, 603; (b) K. Kawamura, H. Hinou, G. Matsuo, and T. Nakata, *Tetrahedron Lett.*, 2003, **44**, 5259.
24. A similar type of intramolecular Barbier reaction has been reported by Nakata *et al.* (Scheme 17) T. Saito, T. Takeuchi, M. Matsuhashi, and T. Nakata, *Heterocycles*, 2007, **72**, 151.



Scheme 17

25. F. Kido, K. Tsutsumi, R. Murata, and A. Yoshikoshi, *J. Am. Chem. Soc.*, 1979, **101**, 6420.
26. L. M. Finkielsztein, J. M. Aguirre, B. Lantano, E. N. Alesso, and G. Y. Moltrasio Iglesias, *Synth. Commun.*, 2004, **34**, 895.
27. For reviews, see: P. N. Confalone and E. M. Huie, *Org. React.*, 1988, **36**, 1420; V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247.
28. (a) O. Duclos, A. Dureault, and J. C. Depezay, *Tetrahedron Lett.*, 1992, **33**, 1059; (b) K. Shishido, K. Umimoto, and M. Shibuya, *Heterocycles*, 1994, **38**, 641; (c) A. Nivlet, L. Dechoux, T. L. Gall, and C. Mioskowski, *Eur. J. Org. Chem.*, 1999, 3251; (d) M.–C. P. Yeh, C.–F. Jou, W.-T. Yeh, D.–Y.

Chiu, and N. R. K. Reddy, *Tetrahedron*, 2005, **61**, 493.

29. T. Nakata, Y. Tani, M. Hatozaki, and T. Oishi, *Chem. Pharm. Bull.*, 1984, **32**, 1411.
30. L. A. Paquette, C. K. Seekamp, A. L. Kahane, D. G. Hilmey, and J. Gallucci, *J. Org. Chem.*, 2004, **69**, 7442.
31. H. Sasaki, H. Yokoe, M. Shindo, M. Yoshida, and K. Shishido, *Heterocycles*, in press.
32. T. Hashimoto, T. Tashiro, M. Sasaki, and H. Takikawa, *Biosci. Biotechnol. Biochem.*, 2007, **71**, 2046.
33. I. Mori, K. Takai, K. Oshima, and H. Nozaki, *Tetrahedron*, 1984, **40**, 4013.
34. (a) E. Sisu, M. Sollogouh, J.-M. Mallet, and P. Sinay, *Tetrahedron*, 2002, **58**, 10189; (b) C. Jia, Y. Zhang, and L. Zhang, *Tetrahedron: Asymmetry*, 2003, **14**, 2193.
35. A. A. Mahmoud, *Planta Medica*, 1998, **64**, 724.
36. B. Pinel, A. Landreau, D. Seraphin, G. Larcher, J.-P. Bouchara, and P. Richomme, *J. Enz. Inhibit. & Med. Chem.*, 2005, **20**, 575.
37. (a) K. Fugami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1987, **28**, 809; (b) K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2050.
38. (a) S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc., Chem. Commun.*, 1983, 469; (b) E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
39. (a) J. C. Gilbert and U. Weerasooriya, *J. Org. Chem.*, 1982, **47**, 1837; (b) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, 1971, **36**, 1379.
40. A. A. Devreese, P. J. DeClercq, and M. Vandewalle, *Tetrahedron Lett.*, 1980, **21**, 4767.
41. J. E. Little, M. W. Foote, and D. B. Johnstone, *Arch. Biochem.*, 1950, **27**, 247.
42. (a) T. A. Geissman, P. G. Deuel, E. K. Bonde, and F. A. Addicott, *J. Am. Chem. Soc.*, 1954, **76**, 685; (b) P. G. Deuel and T. A. Geissman, *J. Am. Chem. Soc.*, 1957, **79**, 3778.
43. B. Pinel, G. Audo, S. Mallet, M. Lavault, F. D. L. Poype, D. Seraphin, and P. Richomme, *J. Chromatogr. A*, 2007, **1151**, 14.
44. H. H. Yoon, H. J. Lim, H. J. Lee, H.-D. Kim, R. Jeon, and J.-H. Ryu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2179.
45. H. Yokoe, M. Yoshida, and K. Shishido, *Tetrahedron Lett.*, 2008, **49**, 3504.
46. N. Hanryu, T. Aoki, T. Mino, M. Sakamoto, and T. Fujita, *Tetrahedron: Asymmetry*, 2000, **11**, 4127.
47. S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, 1991, **32**, 3017.
48. P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485.
49. P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 1974, **39**, 120.
50. K. Matsuo, H. Yokoe, K. Shishido, and M. Shindo, *Tetrahedron Lett.*, 2008, **49**, 4279.

Dr. Kozo Shishido was born in Miyagi prefecture in 1946, and received his B.S. in 1970 and Ph.D. in 1976 from Tohoku University under the direction of the late Professor Tetsuji Kametani. Afer he was appointed as Assistant Professor at Tohoku University in 1972, he joined the late Professor A. I. Scott's group at Texas A&M University and then Professor M. E. Jung's group at University of California, Los Angeles as a postdoctoral fellow from 1978-1980. He then moved to University of Tokushima as Associate Professor in 1989. In 1994, he rose to the rank of Full Professor at University of Tokushima, where he is currently Professor of the Graduate School of Pharmaceutical Sciences. His research interest is in the area of total synthesis of biologically significant molecules.