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Synthetic studies on biscembranoids: asymmetric total synthesis of methyl sarcoate

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Abstract—The asymmetric total synthesis of a marine natural product, methyl sarcoate, has been achieved featuring the asymmetric Michael addition, the dithiane coupling, the Kosugi–Migita–Stille coupling, and the ring-closing metathesis.

Biscembranoids (tetraterpenoids) isolated from soft corals are unique members of marine natural products and considered to be biogenetically formed by a Diels–Alder reaction of two cembranes (Fig. 1). So far the following six biscembranoids have been isolated from several soft corals: methyl isosartortuoate,[1] methyl sartortuoate,[2] methyl sarcophytoate (**1**),[3] methyl chlorosarcophytoate,[3] methyl neosartortuate acetate (**2**),[4] and nyalolide.[5] Methyl sarcoate (**3**) is the common dienophile unit of **1**, **2**, and methyl chlorosarcophytoate, and was isolated from the original corals,[4,6] which produce these biscembranoids. In contrast, probably because of its highly reactive nature, the diene unit has been isolated only from the soft coral, which produces **2**.[4] Among the six biscembranoids, the absolute configuration was elucidated only in the case of **1** based on the difference CD spectrum.[7] During the course of our synthetic studies of the biscembranoids, we reported the asymmetric total synthesis of the unstable 14-membered diene unit **4** of methyl sarcophytoate (**1**).[8,9] In this letter, we report the first asymmetric total synthesis of the 14-membered dienophile unit, methyl sarcoate (**3**), of methyl sarcophytoate (**1**).

Figure 2 shows the synthetic plan of methyl sarcoate (**3**). The C13–C14 bond would be constructed by the dithiane coupling of the C10–C13 dithiane **5** with the C1–C3, C14 allyl bromide **6**. After elongation at the C10 position using the Grignard reagent **7**, the C3–C4 bond would be constructed by the Kosugi–Migita–Stille coupling between tributyl(vinyl)tin **8** and the C1–C3, C9–C14 acid chloride derived from the above elongation product. The final cyclization between the C8 and C9 positions would be realized by the Grubbs ring-closing metathesis.

The synthesis of the C10–C13 dithiane **5**, which has the sole chiral center found in methyl sarcoate (**3**), commenced with the α,β-unsaturated ester **9** possessing the chiral aminal function (Scheme 1).[10] Asymmetric addition of *i*-PrMgCl to **9** in the presence of a catalytic amount of CuI followed by acidic hydrolysis of the aminal function afforded the chiral aldehyde **10**[10,11] in 60% yield. The optical purity and the absolute configuration of **10** were determined as follows. Pentenylation[12] of **10** gave a 4:1 mixture of lactone **11**, the major diastereomer of which was transformed into **12a** and **12b** in three steps. The modified Mosher ester analysis[13] of them revealed the optical purity and the absolute configuration of the hydroxy-substituted carbon to be more than 95% and *R*, respectively. In addition, the relative configuration of both diastereomers of **11** was determined by the transformation to the known, separable lactones **13a**[14] and **13b**.[15] These results confirmed the optical purity and the absolute configuration of **10** to be more than 95% and *S*, respectively. Dithioacetalization

Keywords: Biscembranoid; Methyl sarcoate; Dithiane; Kosugi–Migita–Stille coupling; Ring-closing metathesis.
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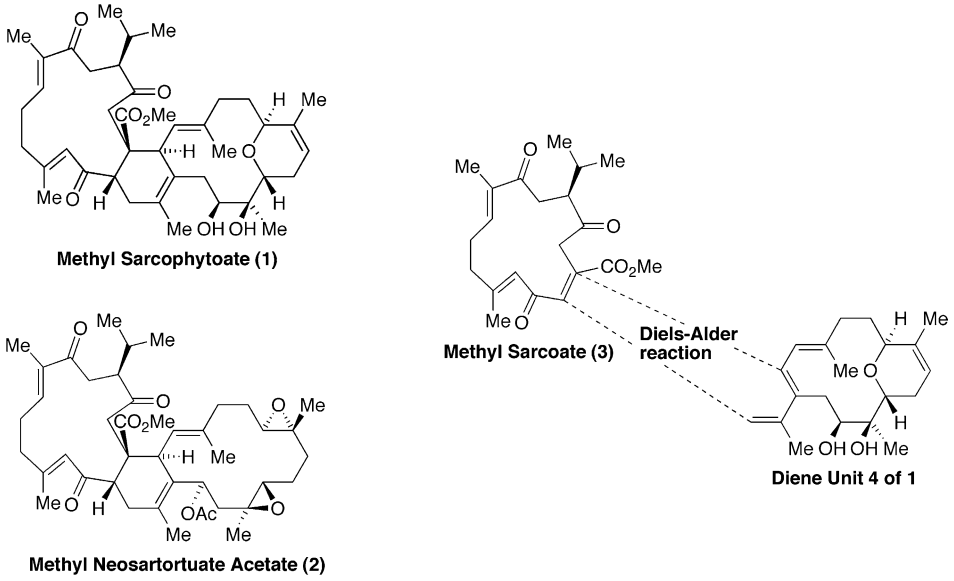


Figure 1.

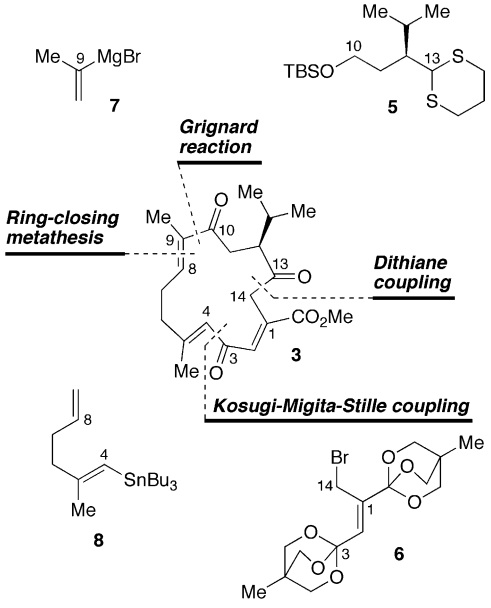


Figure 2. Synthetic plan of methyl sarcoate (**3**).

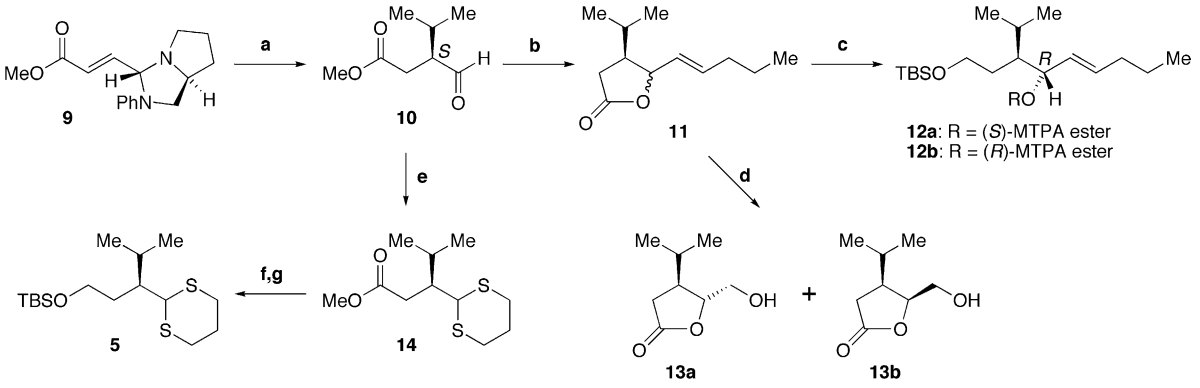
(1,3-propanedithiol, $BF_3{\cdot}OEt_2$) of **10** gave **14** in 64% yield, which was reduced with $LiAlH_4$ (94% yield) and the resulting alcohol was silylated with TBSCl and imidazole to afford the desired dithiane **5** in 92% yield.

The C1–C3, C14 allyl bromide **6** was synthesized from mesaconic acid (**15**) (Scheme 2). Acid chloride derived from **15** [$(COCl)_2$, cat DMF][16] was treated with (3-methyloxetan-3-yl)methanol to give ester **16** (92% yield), which was transformed into orthoester **17** by treatment with $BF_3{\cdot}OEt_2$ in 61% yield.[17] Allylic bromination of **17** with NBS and BPO afforded allyl bromide **6** in 68% yield.

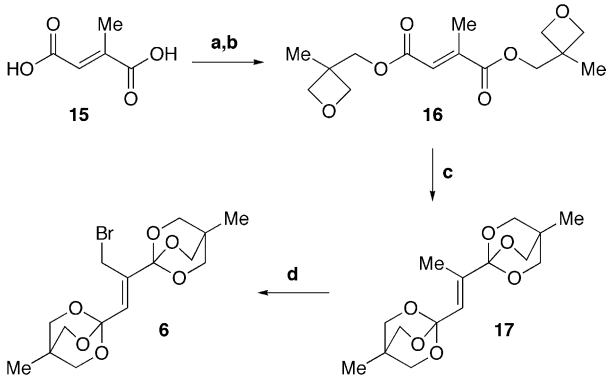
The first crucial coupling between dithiane **5** and allyl bromide **6** was reproducibly realized by our recently-reported methodology[18] (Scheme 3). Dithiane **5** (2 equiv) was treated in THF with *n*-BuLi (2.4 equiv)–Bu_2Mg (0.6 equiv) at rt for 0.5 h; to this was added allyl bromide **6** (1 equiv) at −78 °C and the resulting solution was gradually warmed to 0 °C during a period of 1.5 h, giving the coupling product **18** in 56% yield.[19,20] The orthoester moiety in **18** was converted to the methyl ester by a two-step hydrolysis and methyl ester formation in 84% yield. The resulting **19** was oxidized with IBX[21] to give aldehyde, which was successively subjected to coupling with the vinyl Grignard reagent **7** and IBX oxidation to generate **20** in 60% overall yield. For the sake of introducing the C4–C8 portion, selective hydrolysis of one of the dimethyl ester in **20** was needed. Fortunately, selective hydrolysis of **20** was realized using LiOH (2 equiv) in 2:1 THF–H_2O, producing carboxylic acid **21** in 78% yield as the only monocarboxylic acid. The structure of **21** was confirmed by HMBC NMR analysis.

The C4–C8 vinyl stannane **8** was synthesized from 4-pentyn-1-ol (**22**) (Scheme 4). Methylalumination of **22** [Cp_2ZrCl_2 (0.5 equiv), Me_3Al (3 equiv), $ClCH_2CH_2Cl$] followed by iodination [I_2 (1.2 equiv), THF] gave vinyl iodide **23** in 74% yield.[22] Lithiation of **23** with *n*-BuLi (2.4 equiv) in ether followed by treatment with *n*-Bu_3SnCl (2.4 equiv) gave vinyl stannane **24** in 72% yield. Oxidation of **24** with TPAP–NMO[23] followed by methylenation gave vinyl stannane **8** in 68% yield.

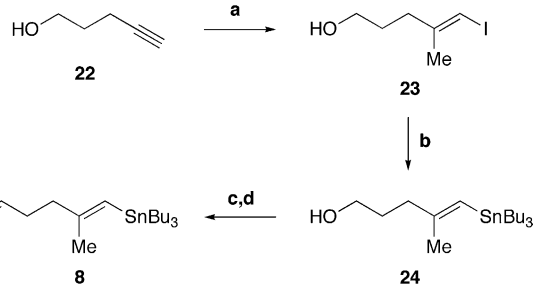
The next crucial step was the Kosugi–Migita–Stille coupling[24] of the C1–C3, C9–C14 acid chloride **25** (derived from **21**) with the C4–C8 vinyl stannane **8** (Scheme 5). Carboxylic acid **21** was transformed into acid chloride **25** with *n*-BuLi (1 equiv) and $(COCl)_2$, which was subjected to the Kosugi–Migita–Stille coupling. The relevant results of this coupling are listed in Table 1. When $Pd(PPh_3)_4$ was used as a catalyst,[25] only the decarbonylation product **27** was obtained in low yield (entry 1). The presence of CO[26] at atmospheric pressure did not affect the result (entry 2). The combination of $Pd(OAc)_2$ and *n*-Bu_3P[27] produced the successful results



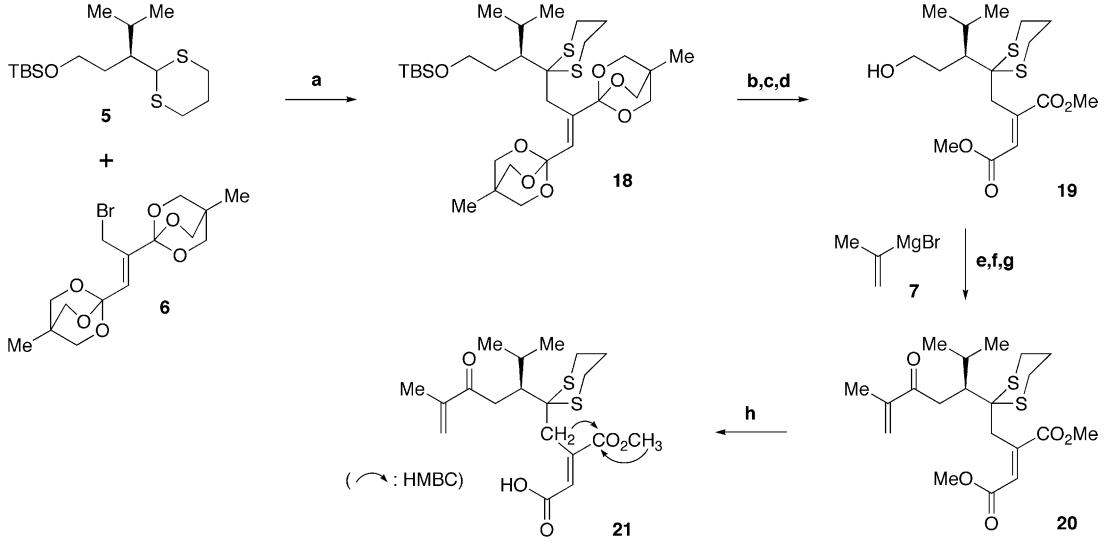
Scheme 1. Synthesis of dithiane **5**. Reagents and conditions: (a) *i*-PrMgCl, cat CuI, ether, −78 °C, 3 h, then 2% aqueous HCl, rt, 1 h, 60%; (b) 1-pentyne, $Cp_2Zr(H)Cl$, CH_2Cl_2, rt, 10 min, then Me_2Zn, −65 to 0 °C, 5 min, then **10** in CH_2Cl_2, rt, 2 h, 82%; (c) (i) $LiAlH_4$, THF, 0 °C, 1 h, 90%; (ii) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 74%, the diastereomers were separated by silica-gel column chromatography; (iii) to **12a**: (*R*)-(−)-MTPA chloride, DMAP, Et_3N, CH_2Cl_2, rt, 2 h, 100%; to **12b**: (*S*)-(+)-MTPA chloride, DMAP, Et_3N, CH_2Cl_2, rt, 2 h, 100%; (d) O_3/O_2, MeOH, −78 °C, 10 min, then Me_2S, −78 to 0 °C, 1 h, then $NaBH_4$, 0 °C, 0.5 h, 55% of **13a**, 14% of **13b**; (e) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 2 h, 64%; (f) $LiAlH_4$, THF, 0 °C, 2 h, 94%; (g) TBSCl, imidazole, CH_2Cl_2, rt, 1 h, 92%. Cp = cyclopentadienyl, TBS = *tert*-butyldimethylsilyl, MTPA = 3,3,3-trifluoro-2-methoxy-2-phenylpropionyl, DMAP = 4-dimethylaminopyridine.



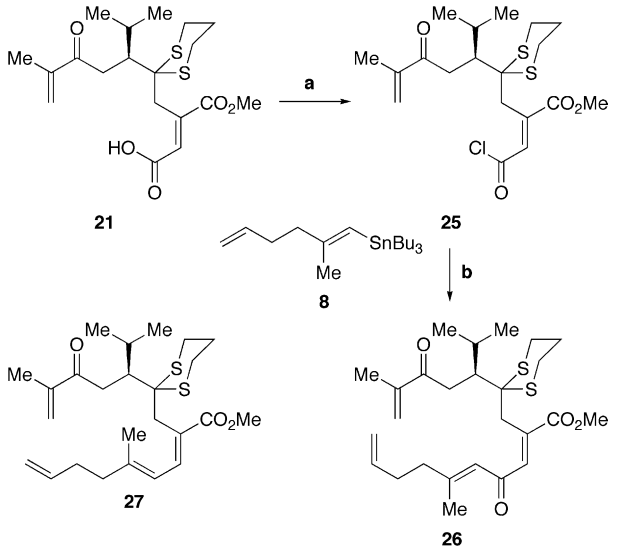
Scheme 2. Synthesis of allyl bromide **6**. Reagents and conditions: (a) $(COCl)_2$, cat DMF, toluene, rt, 3 h; (b) (3-methyloxetan-3-yl)methanol, pyridine, 0 °C to rt, 12 h, 92% (two steps); (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 24 h, then Et_3N, rt, 1 h, 61%; (d) NBS, cat BPO, benzene, reflux, 3 h, 68%. NBS = *N*-bromosuccinimide, BPO = benzoyl peroxide.



Scheme 4. Synthesis of vinyl stannane **8**. Reagents and conditions: (a) Cp_2ZrCl_2 (0.5 equiv), Me_3Al (3 equiv), $ClCH_2CH_2Cl$, rt, 12 h, then I_2 (1.2 equiv) in THF, 0 °C, 0.5 h, 74%; (b) *n*-BuLi (2.4 equiv), ether, −78 °C, 6 h, then *n*-Bu_3SnCl (2.4 equiv), −78 °C to rt, 1.5 h, 72%; (c) cat TPAP, NMO, MS4AP, CH_2Cl_2, rt, 0.5 h, 76%; (d) Ph_3PMeBr, *n*-BuLi, THF, −30 °C to rt, 1 h, 90%. TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, MS4AP = molecular sieves 4 Å powder.



Scheme 3. Synthesis of carboxylic acid **21**. Reagents and conditions: (a) **5** (2 equiv), *n*-BuLi (2.4 equiv)-Bu_2Mg (0.6 equiv), THF, rt, 0.5 h, then **6** (1 equiv) in THF, −78 to 0 °C, 1.5 h, 56%; (b) 1.5 mM aqueous H_2SO_4, MeOH, rt, 3 h, 97%; (c) LiOH, 1:1 MeOH–H_2O, rt, 30 h; (d) CH_2N_2 in ether, MeOH, rt, 10 min, 87% (two steps); (e) IBX, 3:1 THF–DMSO, rt, 2 h, 96%; (f) **7** (2 equiv) in THF, ether, −40 °C, 0.5 h; (g) IBX, 3:1 THF–DMSO, rt, 6 h, 62% (two steps); (h) LiOH (2 equiv), 2:1 THF–H_2O, rt, 2 h, 78%. IBX = *o*-iodoxybenzoic acid.



Scheme 5. Kosugi–Migita–Stille coupling of **25** with **8**. Reagents and conditions: (a) **21**, *n*-BuLi (1 equiv), THF, −78 to 0 °C, 5 min, then $(COCl)_2$, 0 °C to rt, 0.5 h; (b) **25** (1 equiv), **8** (2 equiv), atmospheric pressure of CO, $Pd(OAc)_2$ (10 mol %), n-Bu_3P (10 mol %), benzene, rt, 1 h, 71%.

(entries 3–6); the best conditions so far was entry 6, affording **26** in 71% yield.

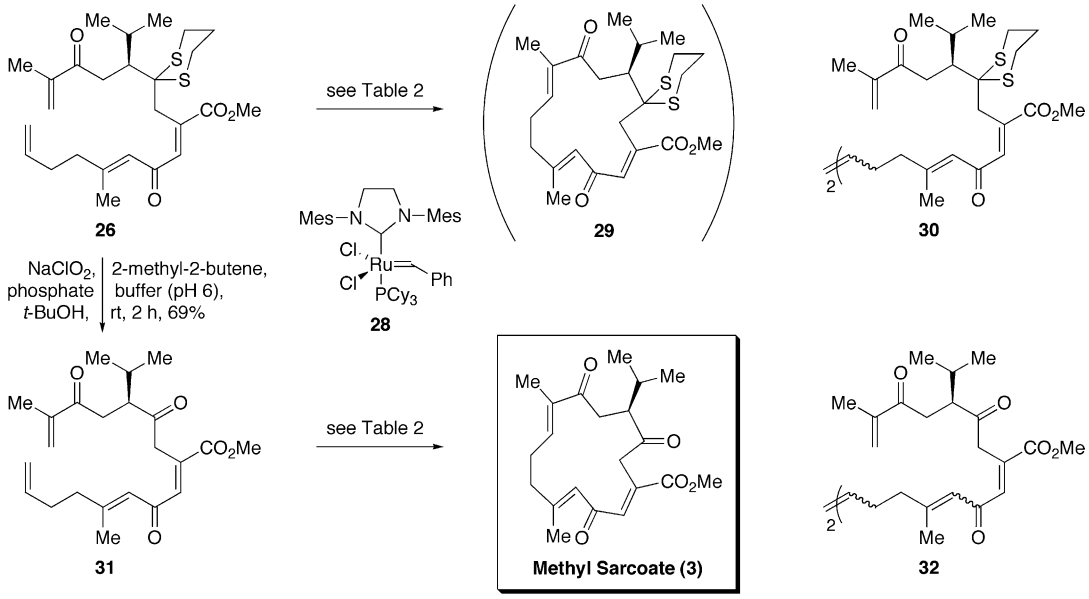
The final crucial step was the ring-closing metathesis (Scheme 6). Initial attempts using dithiane **26** and a catalytic amount of the Grubbs second-generation catalyst **28**[28] resulted in failure; not the desired product **29** but the dimer **30** was obtained as a mixture of the stereoisomers (Table 2, entries 1 and 2). Therefore, the dithiane group in **26** was transformed into the carbonyl group using our recently-reported method,[29] affording **31** in 69% yield. The ring-closing metathesis of **31** in the presence of a catalytic amount of **28** also failed; the dimer **32** as a major product and only a trace amount of methyl sarcoate (**3**) were obtained (Table 2, entries 3 and 4). The best conditions obtained to date were using a stoichiometric amount of the Grubbs catalyst **28**, producing methyl sarcoate (**3**) in 43% yield (Table 2, entry 6). The synthetic methyl sarcoate (**3**) was identical (^{1}H NMR, ^{13}C NMR, CD[30]) to the natural methyl sarcoate (**3**).[6]

In summary, we have synthesized the 14-membered dienophile unit, methyl sarcoate (**3**), of methyl sarcophytoate (**1**). The success of the asymmetric synthesis of **3**

Table 1. Kosugi–Migita–Stille coupling between **25** and **8**

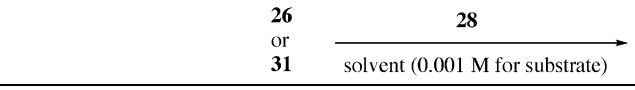
25 (1.0 equiv) + **8** (2.0 equiv) → **26** + **27**
catalyst (10 mol% for **25**), solvent (0.1 M for **25**)

Entry	Catalyst	Solvent	Atmosphere	Temperature (°C)	Time (h)	Yield (%)	
						26	**27**
1	$Pd(PPh_3)_4$	THF	Ar	50	36	0	28
2	$Pd(PPh_3)_4$	THF	CO	50	16	0	27
3	1:1 $Pd(OAc)_2$–n-Bu_3P	THF	CO	rt	12	30	0
4	1:1 $Pd(OAc)_2$–n-Bu_3P	THF	Ar	rt	12	36	Trace
5	1:1 $Pd(OAc)_2$–n-Bu_3P	Toluene	CO	rt	3	43	0
6	1:1 $Pd(OAc)_2$–n-Bu_3P	Benzene	CO	rt	1	71	0



Scheme 6. Final stage.

Table 2. Ring-closing metathesis of **26** and **31**



Entry	Substrate	Solvent	**28** (mol %)	Temperature (°C)	Time (h)	Yield (%)				Recovered substrate
						29	**30**	**3**	**32**	
1	**26**	CH_2Cl_2	15	40	12	0	38			58
2	**26**	Toluene	15	100	6	0	19			64
3	**31**	CH_2Cl_2	15	40	24			Trace	32	58
4	**31**	Toluene	15	100	12			Trace	24	54
5	**31**	CH_2Cl_2	100	40	20			13	27	Trace
6	**31**	Toluene	100	100	0.5			43	0	0

confirmed the absolute configuration of not only **3** but also **1**.[6,7] Synthetic studies of the biscembranoid family of marine natural products are now in progress.

Acknowledgements

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References and notes

1. Jingyu, S.; Kanghou, L.; Tangsheng, P.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 177–178.
2. Jingyu, S.; Kanghou, L.; Tangsheng, P.; Longmei, Z.; Qitai, Z.; Xiuyun, L. *Sci. Sinica, Ser. B* **1988**, *31*, 1172–1184.
3. Kusumi, T.; Igari, M.; Ishitsuka, M. O.; Ichikawa, A.; Itezono, Y.; Nakayama, N.; Kakisawa, H. *J. Org. Chem.* **1990**, *55*, 6286–6289.
4. Leone, P. A.; Bowden, B. F.; Carroll, A. R.; Coll, J. C.; Meehan, G. V. *J. Nat. Prod.* **1993**, *56*, 521–526.
5. Feller, M.; Rudi, A.; Berer, N.; Goldberg, I.; Stein, Z.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 1303–1308.
6. Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2917–2918.
7. Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 6595–6596.
8. (a) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Synlett* **1997**, 899–902; (b) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1417–1429.
9. Synthetic studies on biscembranoids by the Xu's group, see: (a) Liao, X.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4641–4644; (b) Gao, Y.; Nan, F.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4811–4813; (c) Hong, Z.; Chen, X.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 485–488; (d) Hong, Z.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 489–491; (e) Liu, P.; Xu, X. *Tetrahedron Lett.* **2004**, *45*, 5163–5166.
10. Asami, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 569–572.
11. $[\alpha]_D^{24}$ +119 (*c* 5.01, ether) [lit.[10] $[\alpha]_D^{18}$ +114 (*c* 5.22, ether)].
12. Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197–5200.
13. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
14. The enantiomer of **13a**, see: Blazis, V. J.; Hawkins, E. S.; Baker, D. C. *Carbohydr. Res.* **1994**, *253*, 225–233.
15. Costa, J. S.; Dias, A. G.; Anholeto, A. L.; Monteiro, M. D.; Patrocinio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002–4006.
16. Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653–1658.
17. Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.
18. (a) Ide, M.; Yasuda, M.; Nakata, M. *Synlett* **1998**, 936–938; (b) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491–2499.
19. When the metalation was conducted with only *n*-BuLi, the coupling yield was less than 30%.
20. When each dimethyl, diethyl, and di-*t*-butyl ester was used instead of orthoester **6**, only a complex mixture was obtained.
21. (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022; (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276; (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
22. Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501–502.
23. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
24. Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50.
25. Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423–1424.
26. Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642.
27. Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513–2516.
28. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
29. Ichige, T.; Miyake, A.; Kanoh, N.; Nakata, M. *Synlett* **2004**, 1686–1690.
30. CD (EtOH) λ_{max} 255 ($\Delta\varepsilon$ +20.6), 225 ($\Delta\varepsilon$ −6.4) nm [lit.[6] CD (EtOH) λ_{max} 253 ($\Delta\varepsilon$ +19.6), 223 ($\Delta\varepsilon$ −6.4) nm].