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Total Synthesis of Diterpenoid Steenkrotin A**

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Dedicated to Professors Cheng Ma and Yanguang Wang

Abstract: *A concise and diastereoselective total synthesis of the diterpenoid (±)-steenkrotin A is described for the first time. The strategy mainly features three key ring formations: 1) a rhodium-catalyzed O–H bond insertion followed by an intramolecular carbonyl-ene reaction to build up the tetrahydrofuran subunit; 2) sequential SmI_2-mediated Ueno–Stork and ketyl–olefin cyclizations to construct the [5,7] spirobicyclic skeleton; and 3) an intramolecular aldol condensation/vinylogous retro-aldol/aldol sequence to form the final six-membered ring with inversion of the relative configuration at the C7 position.*

Croton steenkampianus Gerstner (Euphorbiaceae) is a shrub or tree endemic to central Africa and eastern parts of southern Africa.[1] With "Marsh Fever-berry" and "Tonga Croton" as the common names, many species of this genus have been widely used in folk medicine to treat a variety of illnesses such as coughs, fever, malaria, and rheumatism. In 2008, Hussein and co-workers isolated two novel diterpenoids from the extract of leaves of *C. steenkampianus*, and were named steenkrotins A and B (**1** and **2**, respectively; Figure 1).[2]

Structurally, (±)-steenkrotin A (**1**) possesses an intricate [3,5,5,6,7] pentacyclic carbon framework containing a sterically congested hydroxytetrahydrofuran subunit, while steenkrotin B (**2**) features an unusual [5,6,6,7] tetracyclic skeleton embedded with an endoperoxide moiety. Both of these molecules contain eight stereogenic centers, of which six are contiguous, including one all-carbon quaternary center. The intriguing structures as well as the potentially important biological activities rendered **1** and **2** attractive targets for synthetic studies. Previously, we reported an efficient synthetic route to the angularly fused [5,6,7] tricyclic core structure of **1** and **2** through an intramolecular nitrile oxide/alkene [3+2] cycloaddition strategy.[3] Herein, we describe our recent efforts culminating in a concise and diastereoselective total synthesis of (±)-steenkrotin A (**1**).

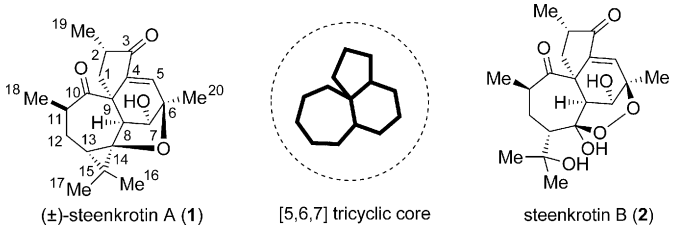
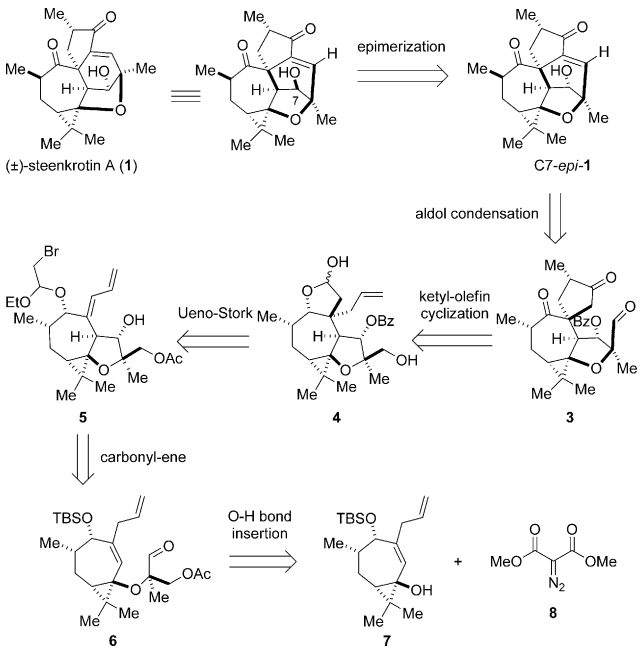


Figure 1. Steekrotins A (**1**) and B (**2**), and their [5,6,7] tricyclic core.

Our retrosynthetic analysis depicts a systematic approach in the deconstruction of the complex fused pentacyclic system (Scheme 1). We rationalized that **1** might be synthesized through the late-stage epimerization of C7-*epi*-**1**. For its construction, we envisaged an intramolecular aldol condensation[4] of the diketone aldehyde **3** to forge the six-membered ring of the molecule. The spirobicyclic structure of **3** could be constructed from the [3,5,7] tricycle **5** by the successive radical-initiated Ueno–Stork[5] and ketyl–olefin cyclizations.[6] An intramolecular carbonyl-ene reaction[7] of the [3,7] bicyclic aldehyde **6** was then planned to install the desired tetrahydrofuran subunit. Finally, the essential aldehyde **6**



Scheme 1. Retrosynthetic analysis of (±)-steenkrotin A (**1**).

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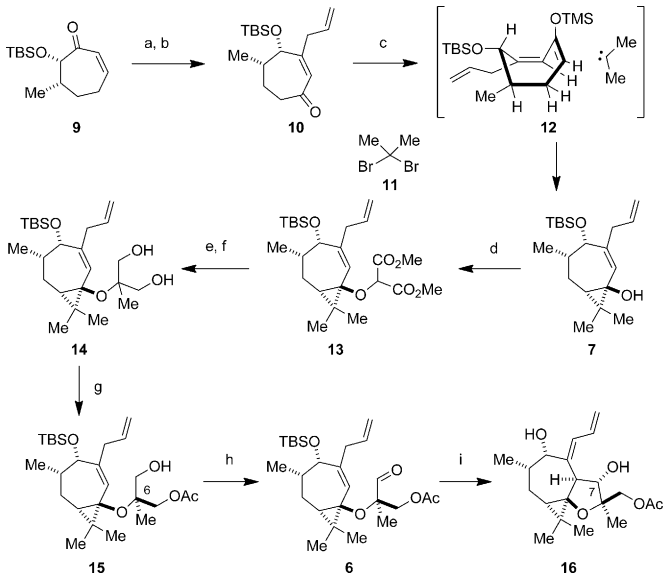
could be obtained from the [3,7] bicyclic alcohol **7** and readily available diazomalonic ester **8** by a rhodium-catalyzed O–H bond insertion,[8] followed by selective substrate-controlled transformations of the two esters.

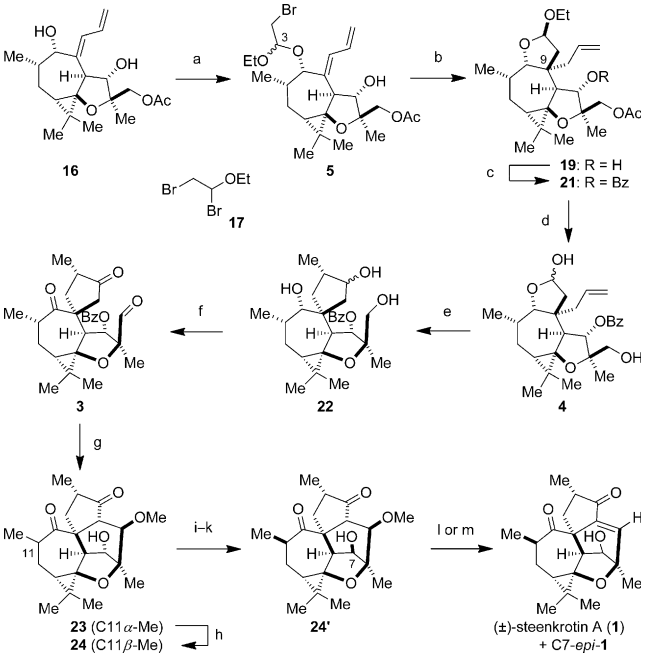
The synthetic endeavor commenced with construction of the [3,5,7] tricycle **16** (Scheme 2). The enone **9** was readily



Scheme 2. Construction of the [3,5,7] tricycle **16**. Reagents and conditions: a) allyl bromide (1.5 equiv), Li (1.3 equiv), THF, 0→25 °C, 2 h; b) PCC (2.0 equiv), SiO_2 (5.0 equiv), CH_2Cl_2, 0→25 °C, 24 h, 72% (2 steps); c) TMSOTf (1.0 equiv), Et_3N (1.5 equiv), CH_2Cl_2, −40 °C, 30 min; then **11** (3.8 equiv), *n*BuLi (2.5 M in hexanes, 3.8 equiv), Et_2O, −78→25 °C, 34 h, 70%; d) $[Rh_2(OAc)_4]$ (0.05 equiv), **8** (2.0 equiv), benzene, 55 °C, 30 min, 73%; e) NaH (2.0 equiv), MeI (5.0 equiv), THF, 0→25 °C, 3 h; f) $LiAlH_4$ (2.0 equiv), THF, 0→25 °C, 1 h, 72% (2 steps); g) Ac_2O (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0→25 °C, 3 h, 91%, 10:1 d.r. at C6; h) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 25 °C, 1 h, 95%; i) HF·py (10 equiv), MeCN, 25 °C, 6 h, 90%. PCC = pyridinium chlorochromate, py = pyridine, THF = tetrahydrofuran, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

prepared on large scale by Rubottom oxidation[9] of the silyl dienol ether derived from commercially available 6-methyl-2-cyclohepten-1-one (see the Supporting Information for a detailed procedure). 1,2-Addition of allyllithium to **9** and subsequent Dauben–Michno oxidative rearrangement[10] afforded **10** in 72% yield over two steps. Benefiting from the preferred boat transition state of **12**,[11] in situ generated dimethylcarbene[12] added exclusively to the less hindered convex face, and afforded **7** in 70% yield as a single diastereomer. To our delight, carbenoid O–H insertion[13] of **7** and **8**, catalyzed by $[Rh_2(OAc)_4]$, proceeded smoothly to give the expected diester **13** in 73% yield. After converting **13** into the diol **14** through methylation and reduction (76% yield over the two steps), the two hydroxy groups were successfully differentiated by a substrate-controlled acylation, thus leading to the monoacetate **15** in 91% yield (10:1 d.r. at C6). The minor isomer, C6-*epi*-**15**, could be recycled by treatment with K_2CO_3/MeOH to deliver **14** in quantitative yield. Dess–Martin oxidation of **15** led to **6** in 95% yield, thus setting the stage for the anticipated intramolecular carbonyl-ene cyclization. After extensive investigation, HF·py was found to be the most suitable reagent. Under the optimized reaction conditions (HF·py, 10 equiv), the desired **16** was obtained in 90% yield with concomitant desilylation taking place after prolonged reaction time. Other acids[14] such as $BF_3{\cdot}Et_2O$, TMSOTf, Me_2AlCl, $EtAlCl_2$, $Sc(OTf)_3$, $SnCl_4$, $TiCl_4$, CF_3SO_3H, and aq. HCl either caused substantial decomposition of **6** or gave a large amount of C7-*epi*-**16**.[15]

Encouraged by the rapid assembly of **16**, we then focused on further core modifications for the synthesis of **1**. As depicted in Scheme 3, regioselective alkylation of **16** with the dibromoacetal **17** using $PhNMe_2$ gave **5** as a 1.5:1 mixture of diastereomers in 95% yield. To the best of our knowledge, the Ueno–Stork cyclization on conjugated diene structures has not been well studied.[16] In view of the cycloheptane ring conformation of the structurally related TBS ether **18**, which was obtained during our model studies (ORTEP drawing,



Scheme 3. Total synthesis of (±)-steenkrotin A (**1**). Reagents and conditions: a) **17** (2.0 equiv), $PhNMe_2$ (3.0 equiv), CH_2Cl_2, 25 °C, 2 h, 95%, 1.5:1 d.r. at C3; b) SmI_2 (0.1 M in THF, 2.0 equiv), HMPA (8.0 equiv), *t*BuOH (1.2 equiv), THF, 25 °C, 45 min, **19** (50%), **20** (35%); c) Bz_2O (1.2 equiv), Et_3N (2.0 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 30 min, 95%; d) *p*-TsOH (1.0 equiv), acetone/H_2O (4:1), 60 °C, 6 h, 86%, 4:1 d.r. at C3; e) SmI_2 (0.1 M in THF, 2.0 equiv), HMPA (4.0 equiv), THF, 50 °C, 6 h, 90%, 5:1 d.r. at C3; f) Dess–Martin periodinane (5.0 equiv), $NaHCO_3$ (10.0 equiv), CH_2Cl_2, 25 °C, 1 h, 75%; g) KOH (5.0 equiv), benzene, 80 °C, 2 h; then the addition of MeOH, 25 °C, 1 h, 80% (**23**/**24** 6.3:1); h) DBU (2.0 equiv), toluene, 50 °C, 5 h, 92%; i) TPAP (0.2 equiv), NMO (2.5 equiv), CH_2Cl_2, 25 °C, 30 min, 90%; j) $NaBH_4$ (5.0 equiv), MeOH, 0→25 °C, 15 min; k) PCC (4.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 64% (2 steps); l) LiOH (10.0 equiv), toluene, 110 °C, 4 h, **1** (83%), C7-*epi*-**1** (4%); m) KOH (5.0 equiv), benzene, 80 °C, 2 h, **1** (35%), C7-*epi*-**1** (18%). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-(*N*,*N*′-dimethylamino)pyridine, NMO = 4-methylmorpholine *N*-oxide, HMPA = hexamethylphosphoric triamide, TPAP = tetrapropylammonium perruthenate, TsOH = toluene-sulfonic acid.

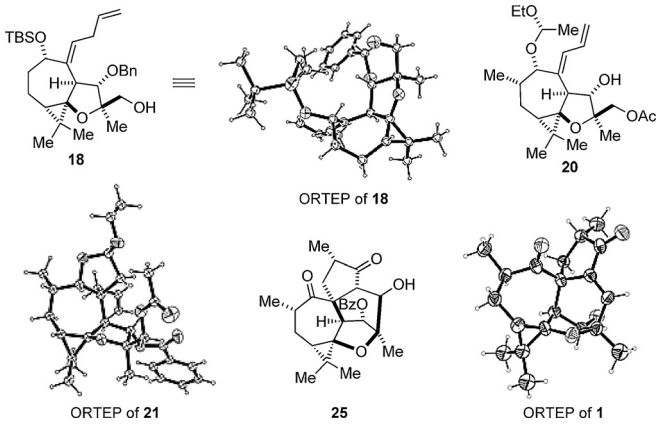


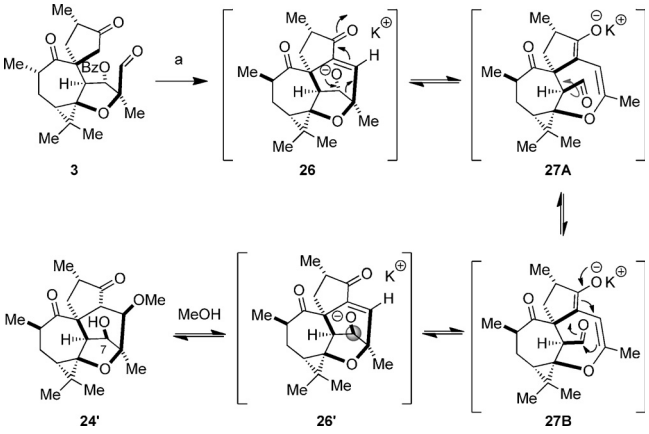
Figure 2. Structures of compounds **18**, **20**, **21**, **25**, and **1**.

Figure 2),[17] we envisioned that the subsequent Ueno–Stork cyclization of **5** would take place on the pseudoconcave face of the *cis*-fused oxabicyclo[5.3.0]decane, thus leading to the construction of the quaternary center at C9 with desired relative configuration. After examination of the reaction conditions (initiator, temperature, addition protocol),[18] we were pleased to find that the 5-*exo*-*trig* radical cyclization of the C3β-isomer of **5** occurred smoothly by slow addition of SmI_2 and HMPA in the presence of *t*BuOH to afford the tetracycle **19** as a single diastereomer in 50% yield, together with **20** (35% yield), which resulted from reductive debromination of the C3α-isomer of **5**. The latter product could be recycled under acidic conditions to afford **16** (*p*-TsOH, acetone/H_2O, 60°C, 1 h, 97% yield). The relative stereochemistry of **19** was unambiguously determined by X-ray crystallographic analysis of its benzoate **21** (ORTEP drawing, Figure 2).[17] Hydrolysis of both the acetal and acetate moieties of **21** delivered **4** in 86% yield (4:1 d.r.), and was immediately transformed into the [5,7] spirobicycle **22** (90% yield, 5:1 d.r. at C3) through a SmI_2-mediated ketyl–olefin cyclization. After oxidation to **3**, the challenging intramolecular aldol condensation was then investigated.

Screening of the reaction conditions revealed that the aldol condensation proceeded well with KOH in benzene, and subsequent removal of the benzoyl group in methanol gave rise to a 6.3:1 mixture of the Michael adducts **23** and **24** in 80% combined yield. In contrast, the alcohol **25** (Figure 2) was formed predominantly upon exposure of **3** to acids (e.g., *p*-TsOH, PPTS, aq. HCl), and did not undergo elimination under various investigated conditions. After DBU-induced C11 epimerization of **23**, the relative configuration at the C7 position of **24** needed to be inverted. Thus, Ley–Griffith oxidation[19] of **24** led to the corresponding triketone, which was uneventfully converted into **24′** by global 1,2-reduction and selective oxidation in 58% yield over the three steps. Finally, treatment of **24′** with LiOH in refluxing toluene furnished (±)-steenkrotin A (**1**) in 83% yield. Synthetic **1** exhibited ^1H and ^{13}C NMR spectra identical in all respects to those reported for the natural product.[2] Its structure was later unambiguously confirmed by X-ray crystallographic analysis (ORTEP drawing, Figure 2).[17]

Serendipitously, apart from **1**, we also observed formation of trace amounts of C7-*epi*-**1** during the final elimination reaction. An approximate 2:1 mixture of **1** and C7-*epi*-**1** was formed by treating **24′** with KOH in refluxing benzene, albeit in moderate yield. Based on these outcomes, the feasibility of a cascade vinylogous retro-aldol/aldol process[20] was explored to develop a more straightforward route for the synthesis of **1**.

After extensive optimization, we were able to obtain **24** and its C7-diastereomer **24′** as a 1:3.5 mixture in 77% yield through the direct treatment of **3** with K_2CO_3 in refluxing methanol (Scheme 4). Mechanistically, the intramolecular



Scheme 4. Cascade intramolecular aldol condensation/vinylogous retro-aldol/aldol reaction. Reagents and conditions: a) K_2CO_3 (10.0 equiv), MeOH, 65°C, 6 h, **24** (17%), **24′** (60%).

aldol condensation and C11 epimerization are presumed to occur first to generate the intermediate **26**, which then undergoes an oxyanion-initiated vinylogous retro-aldol fragmentation to give the aldehyde **27A**. Rapid equilibration between the conformers **27A** and **27B** by C7–C8 bond rotation, followed by transannular vinylogous aldol cyclization of the latter led to the formation of **26′** with successful inversion of the relative configuration at C7. Michael addition of MeOH to **26** and **26′** then gave rise to **24** and **24′**, respectively. Compared to the six-step transformation from **3** (Scheme 3), **1** was accessed in only two operations with a 50% combined yield by taking advantage of this intramolecular aldol condensation/vinylogous retro-aldol/aldol reaction sequence.[21]

In summary, we have developed a concise and diastereoselective approach for the first total synthesis of the diterpenoid (±)-steenkrotin A. The key steps of the strategy entail a rhodium carbenoid O–H insertion followed by a carbonylene cyclization to construct the sterically congested tetrahydrofuran subunit, two sequential SmI_2-mediated Ueno–Stork and ketyl–olefin cyclizations to install the [5,7] spirobicyclic skeleton, and an intramolecular aldol condensation/vinylogous retro-aldol/aldol reaction sequence to form the final six-membered ring with the concomitant inversion of the relative configuration at C7. Moreover, the asymmetric synthesis of natural (+)-steenkrotin A could be accomplished by the enantioselective construction of **9**[22] for further chemical and biological investigations. These studies are currently underway in our laboratory and will be reported in due course.

Keywords: aldol reaction · carbenoids · natural products · radical reactions · total synthesis

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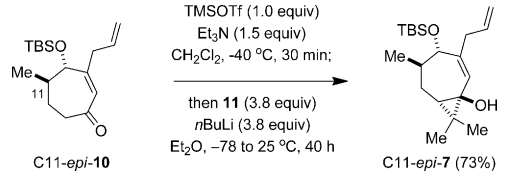
[1] E. Pooley, *The Complete Field Guide to Trees of Natal, Zululand and Transkei*, Natal Flora Publications Trust, Durban, **1993**, pp. 222.
[2] A. M. Adelekan, E. A. Prozesky, A. A. Hussein, L. D. Ureña, P. H. van Rooyen, D. C. Liles, J. J. M. Meyer, B. Rodríguez, *J. Nat. Prod.* **2008**, *71*, 1919.
[3] J. Xuan, S. Pan, Y. Zhang, B. Ye, H. Ding, *Org. Biomol. Chem.* **2015**, *13*, 1643.
[4] For representative examples, see: a) J. Wright, G. J. Drtina, R. A. Roberts, L. A. Paquette, *J. Am. Chem. Soc.* **1988**, *110*, 5806; b) S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1989**, *111*, 8032; c) L. A. Paquette, J. E. Hofferberth, *J. Org. Chem.* **2003**, *68*, 2266; d) N. Itagaki, M. Kimura, T. Sugahara, Y. Iwabuchi, *Org. Lett.* **2005**, *7*, 4185; e) X.-S. Peng, H. N. C. Wong, *Chem. Asian J.* **2006**, *1–2*, 111; f) J. S. Yadav, R. Goreti, S. Pabbaraja, B. Sridhar, *Org. Lett.* **2013**, *15*, 3782.
[5] a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, M. Okawara, *J. Am. Chem. Soc.* **1982**, *104*, 5564; b) G. Stork, R. Mook, Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741; for a comprehensive review, see: c) X. J. Salom-Roig, F. Dénès, P. Renaud, *Synthesis* **2004**, 1903.
[6] a) T. L. Fevig, R. L. Elliott, D. P. Curran, *J. Am. Chem. Soc.* **1988**, *110*, 5064; b) J. G. M. Morton, C. Draghici, L. D. Kwon, J. T. Njardarson, *Org. Lett.* **2009**, *11*, 4492; for a recent review, see: c) M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959.
[7] For reviews, see: a) E. Arundale, L. A. Mikeska, *Chem. Rev.* **1952**, *51*, 505; b) D. R. Adams, S. P. Bhatnagar, *Synthesis* **1977**, 661; c) B. B. Snider, in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, pp. 527; d) M. L. Clarke, M. B. France, *Tetrahedron* **2008**, *64*, 9003.
[8] a) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091; b) D. J. Miller, C. J. Moody, *Tetrahedron* **1995**, *51*, 10811; c) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-VCH, Weinheim, **1998**.
[9] G. M. Rubottom, J. M. Gruber, *J. Org. Chem.* **1978**, *43*, 1599.
[10] W. G. Dauben, D. M. Michno, *J. Org. Chem.* **1977**, *42*, 682.
[11] The preferred boat conformation of **12** (with the equatorial OTBS group) could also be verified by the cyclopropanation of C11-*epi*-**10** under standard reaction conditions, which gave product C11-*epi*-**7** in 73% yield.



[12] a) P. Fischer, G. Schaefer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 863; *Angew. Chem.* **1981**, *93*, 895; b) M. G. B. Drew, L. M. Harwood, A. J. Macías-Sánchez, R. Scott, R. M. Thomas, D. Uguen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2311; *Angew. Chem.* **2001**, *113*, 2373; c) I. Hayakawa, Y. Asuma, T. Ohyoshi, K. Aoki, H. Kigoshi, *Tetrahedron Lett.* **2007**, *48*, 6221; d) T. Ohyoshi, S. Funakubo, Y. Miyazawa, K. Niida, I. Hayakawa, H. Kigoshi, *Angew. Chem. Int. Ed.* **2012**, *51*, 4972; *Angew. Chem.* **2012**, *124*, 5056.
[13] a) A. Padwa, M. M. Sá, *J. Braz. Chem. Soc.* **1999**, *10*, 231; b) J. Gong, G. Lin, W. Sun, C.-C. Li, Z. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 16745.
[14] a) S. C. Welch, C.-Y. Chou, J. M. Gruber, J. M. Assercq, *J. Org. Chem.* **1985**, *50*, 2668; b) A. Toró, A. L'Heureux, P. Deslongchamps, *Org. Lett.* **2000**, *2*, 2737; c) J. T. Williams, P. S. Bahia, J. S. Snaith, *Org. Lett.* **2002**, *4*, 3727; d) Y.-T. Lin, F.-Y. Lin, M. Isobe, *Org. Lett.* **2014**, *16*, 5948.
[15] In our earlier studies, we found that the relative configuration at the C7 position played an important role in the final-stage intramolecular aldol condensation.
[16] P. Metz, J. Stölting, M. Läge, B. Krebs, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2195; *Angew. Chem.* **1994**, *106*, 2275.
[17] CCDC 1046888 (**18**), 1046889 (**21**), and 1048744 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[18] a) T. Yoshimitsu, S. Yanagisawa, H. Nagaoka, *Org. Lett.* **2000**, *2*, 3751; b) M. Inoue, T. Sato, M. Hirama, *J. Am. Chem. Soc.* **2003**, *125*, 10772; c) K. C. Nicolaou, P. K. Sasmal, A. J. Roecker, X.-W. Sun, S. Mandal, A. Converso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3443; *Angew. Chem.* **2005**, *117*, 3509; d) K. C. Nicolaou, P. K. Sasmal, T. V. Koftis, A. Converso, E. Loizidou, F. Kaiser, A. J. Roecker, C. C. Dellios, X.-W. Sun, G. Petrovic, *Angew. Chem. Int. Ed.* **2005**, *44*, 3447; *Angew. Chem.* **2005**, *117*, 3513; e) M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8078; f) G. K. Murphy, T. Shirahata, N. Hama, A. Bedermann, P. Dong, T. C. McMahon, B. M. Twenter, D. A. Spiegel, I. M. McDonald, N. Taniguchi, M. Inoue, J. L. Wood, *J. Org. Chem.* **2013**, *78*, 477.
[19] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625.
[20] For reviews, see: a) G. Appendino in *The Chemistry and Pharmacology of Taxol and its Derivatives, Vol. 22* (Ed. V. Farina), Elsevier, Amsterdam, **1995**, pp. 7; b) G. Casiraghi, F. Zanardi, *Chem. Rev.* **2000**, *100*, 1929; c) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076; for selected examples, see: d) S. Swaminathan, J. P. John, S. Ramachandran, *Tetrahedron Lett.* **1962**, *3*, 729; e) M. Los, A. D. Mighell, *Tetrahedron* **1965**, *21*, 2297; f) P. Jacobi, E. Härle, H. U. Schairer, E. Hecker, *Liebigs Ann. Chem.* **1970**, *741*, 13; g) H. M. Walborsky, S. M. Reddy, *J. Org. Chem.* **1988**, *53*, 4851; h) V. Pinciroli, W. Ceccarelli, D. Fusar-Bassini, M. Menichincheri, N. Mongelli, E. Vanotti, *Tetrahedron Lett.* **1996**, *37*, 9365; i) G. Appendino, I. Fenoglio, D. G. Vander Velde, *J. Nat. Prod.* **1997**, *60*, 464; j) L. O. Zamir, A. D. Cherestes, A. Nikolakakis, F. Sauriol, O. Mamer, *Tetrahedron Lett.* **1999**, *40*, 7917; k) J. N. Payette, T. Honda, H. Yoshizawa, F. G. Favaloro, Jr., G. W. Gribble, *J. Org. Chem.* **2006**, *71*, 416.
[21] In contrast, retreatment of **24** with K_2CO_3/MeOH resulted in the formation of **24** and **24′** in 75% yield as a 1:3.7 mixture.
[22] For the preparation of optically active 6-methyl-2-cyclohepten-1-one, see: a) J. C. McWilliams, J. Clardy, *J. Am. Chem. Soc.* **1994**, *116*, 8378; b) H. Weinmann, E. Winterfeldt, *Synthesis* **1995**, 1097; c) R. B. C. Jagt, R. Imbos, R. Naasz, A. J. Minnaard, B. L. Feringa, *Isr. J. Chem.* **2001**, *41*, 221; d) M. Torihata, T. Nakahata, S. Kuwahara, *Org. Lett.* **2007**, *9*, 2557.

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