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Asymmetric Synthesis of a Chiral Building Block for Cyclopentanoids: A Novel Enantioselective Synthesis of Preclavulone A

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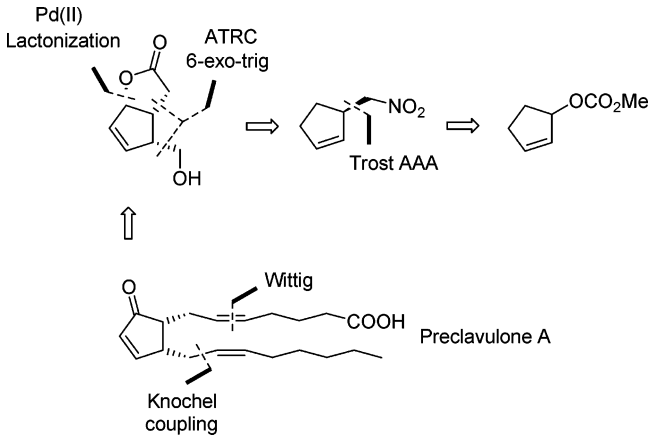

A new asymmetric approach to the hydroxylactone (+)-(3a*R*,4*R*,6a*S*)-4-(hydroxymethyl)-3a,4-dihydro-3*H*-cyclopenta[*b*]furan-2(6a*H*)-one (**1**), a key synthetic building block for cis-1,2-disubstituted five-membered ring derivatives (i.e., isoprostanes, jasmonates, and clavulones), has been described. A remarkable control of the absolute and relative configuration of the three stereocenters was achieved. Thus, the use of the Trost's asymmetric allylic alkylation strategy secured highly enantioenriched (*R*)-3-(nitromethyl)cyclopent-1-ene (**13**), which was smoothly converted to (*R*)-cyclopent-2-enecarboxylic acid (**15**) in excellent yield and high enantiomeric purity (>98% ee). 6-*exo-trig* atom-transfer radical cyclizations of ((*R*)-cyclopent-2-enyl)methyl 2-iodoacetate (**12**) produced exclusively the desired cis-fused δ-lactone (4a*R*,7a*R*)-hexahydro-5-iodocyclopenta[*c*]pyran-3(1*H*)-one (**11**), which was subsequently elaborated to hydroxylactone **1** through a stereocontrolled Pd(II)-mediated lactonization reaction. En route to preclavulone A, a putative elusive intermediate in the biosynthesis of clavulones, the synthetic utility of compound **1** was demonstrated. The key feature in this synthesis was the installation of the lower side chain via the Knochel organozinc sp^3-sp C−C coupling protocol.

Introduction

A wide range of useful synthetic intermediates and a vast number of natural products endowed with a broad spectrum of biological activities contain a cyclopentanoid structural framework. Among them, prostaglandin-like 1,2-cis-disubstituted derivatives, such as epi-jasmonates,[1a] isoprostanes, and neuroprostanes,[1b] have recently raised a considerable interest for their way of formation in living systems via radical species and for their biological and pharmacological importance as oxidative stress markers.[2] Moreover, the synthetic challenge to install the two thermodynamically less stable 1,2-cis-configured side chains, for which classical approaches to prostaglandin congeners cannot be applied, has stimulated several imaginative new routes to compounds of this type.[1b]

(1) (a) Bauer, K.; Grabe, D.; Surburg, H. *Common Fragrance and Flavour Materials*; Wiley-VCH: Weinheim, 2001; p 94. (b) Durand, T.; Guy, A.; Henry, O.; Roland, A.; Bernad, S.; El Fangour, S.; Vidal, J.-P.; Rossi, J.-C. *Chem. Phys. Lipids* **2004**, *128*, 15.

(2) (a) Greco, A.; Minghetti, L.; Levi, G. *Neurochem. Res.* **2000**, *25*, 1357. (b) Fam, S. S.; Morrow, J. D. *Curr. Med. Chem.* **2003**, *10*, 1723.

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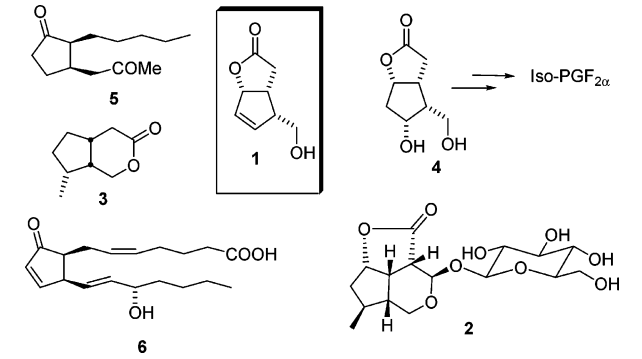
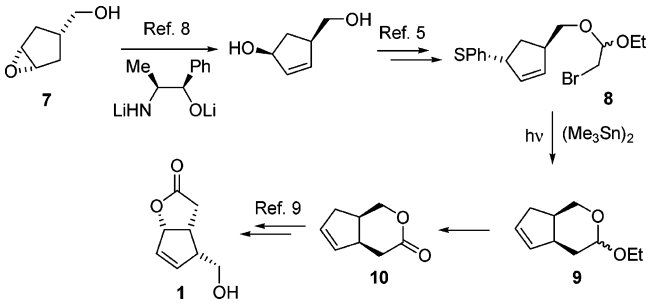


FIGURE 1. Natural cyclopentanoid compounds prepared from lactone **1**.

SCHEME 1



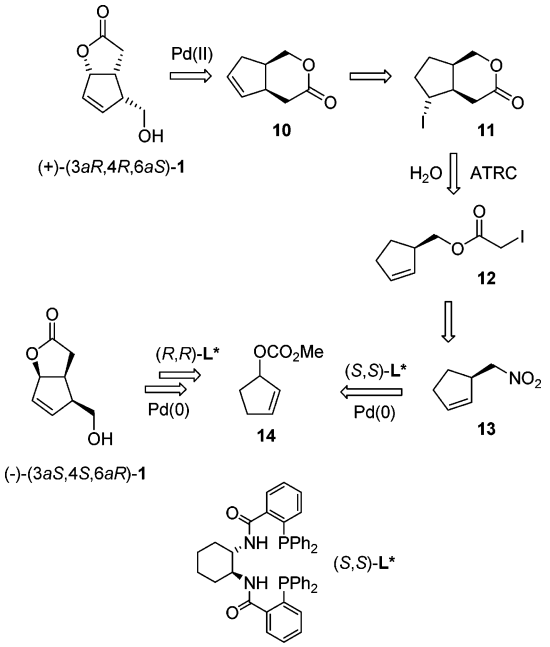
In pursuing the asymmetric synthesis of representative cyclopentanoid natural products, we elected lactone **1** as a key chiral building block. Indeed, compound **1** has shown a high synthetic versatility, as exemplified by our syntheses of iridoids such as semperoside A **2**[3a] and 7-*epi*-boschnialactone **3**,[3b] F_2-isoprostanes[4] via hydroxylactone **4**,[5] perfume component magnolione **5**,[6] and *rac*-15-A_2-isoprostane **6**[6] (Figure 1).

Our first enantioselective synthesis of lactone **1**[5] was based on a 6-*exo*-trigonal radical cyclization of bromoacetal **8** to pyran **9**, whose chirality ultimately was derived from a dilithiate *nor*-ephedrine-mediated desymmetrization of achiral epoxyalcohol **7** (Scheme 1).[8] Subsequently, the bicyclic acetal **9** was oxidized to *δ*-lactone **10**, which gave the isomeric lactone **1** by Pd-induced lactonization of the corresponding sodium carboxylate.[9]

This route to **1**, though streamlined, suffered, however, because of a few drawbacks, such as the use of stoichiometric amounts of the chiral base in the enantioselective step, in addition to toxic stannanes and malodorous sulfur compounds.

Given the importance of **1** in synthesis, we considered it worthwhile to explore other routes to it. In this article, we describe a completely different asymmetric approach to **1** via lactone **10**, which, according to Scheme 2, proceeds through three main steps: (i) the asymmetric Pd-mediated alkylation of

SCHEME 2



cyclopentenol carbonate **14** by nitromethane,[10] (ii) the conversion of the so-obtained nitroderivative **13** into iodoacetate **12**, and (iii) the atom-transfer radical cyclization[11] of **12** to iodolactone **11**. The enantio-differentiating step of the synthetic sequence (**14** → **13**) was thus envisaged to occur by using Trost asymmetric ligands **L***, which, being commercially available in either antipodes, would eventually produce either scalemic form of lactone **1** in an expected high enantiomeric excess.[10] On the other hand, precedents in the literature on 6-*exo-trig* atom-transfer radical cyclizations of iodoacetates indicated a strong preference for the formation of cis-fused *δ*-lactone ring,[11] thus favoring the required stereochemistry in the iodo adduct **11**.

Here we detail our synthesis of the (+)-(3a*R*,4*R*,6a*S*)-enantiomer of lactone **1**, which was subsequently used as a starting material in a novel stereoselective total synthesis of (−)-(8*R*,12*R*)-preclavulone A (**24**) (vide infra).

Results and Discussion

As anticipated, exposure of cyclopentenyl carbonate **14**[12] to nitromethane under Trost's asymmetric alkylation condition (Pd_2dba_3, BSA, (*S*,*S*)-**L***)[10] delivered the expected configured (*R*)-nitroderivate **13**, in 93% isolated yield and 98% ee (Scheme 3).

The nitromethyl functionality of compound **13** was then converted into the corresponding carboxylic acid **15** through a stereoconservative procedure, by using $NaNO_2$ as the oxidant of choice in a mixture of AcOH and DMSO (35−38 °C, 10 h, 88%).[13]

The optical rotation of compound **15**, $[\alpha]_D^{20}$ +260° (*c* 0.55, CH_2Cl_2), finely matched that of an enantiopure sample of (+)-

(3) (a) Piccinini, P.; Vidari, G.; Zanoni, G. *J. Am. Chem. Soc.* **2004**, *126*, 5088. (b) Zanoni, G.; Agnelli, F.; Meriggi, A.; Vidari, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1779.

(4) Rokach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis* **1998**, 569.

(5) Zanoni, G.; Re, S.; Meriggi, A.; Castronovo, F.; Vidari, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1785.

(6) Porta, A.; Vidari, G.; Zanoni, G. *J. Org. Chem.* **2005**, *70*, 4876.

(7) Zanoni, G.; Porta, A.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 4346.

(8) Hodgson, D. M.; Gibbs, A. R.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3579.

(9) Zanoni, G.; Porta, A.; Meriggi, A.; Franzini, M.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 6064.

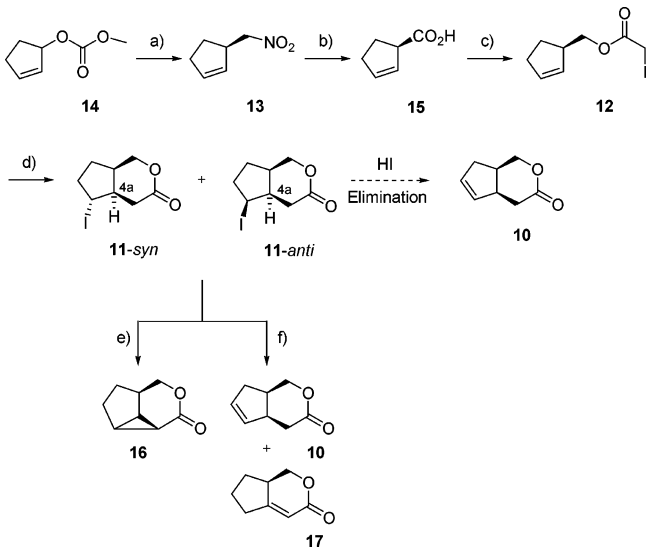
(10) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122.

(11) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041.

(12) Genet, J.-P.; Juge, S.; Achi, S.; Mallart, S.; Montes, J. R.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.

(13) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234.

SCHEME 3[a]

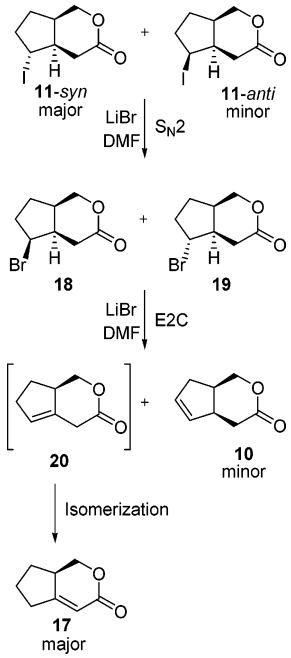


[a] Reagents and conditions: (a) $MeNO_2$, Pd_2dba_3 (0.03 equiv), (*S*,*S*)-**L*** (0.08 equiv), BSA, CH_2Cl_2, rt, 1 h, 93%; (b) $NaNO_2$ (4 equiv), AcOH (10 equiv), DMSO, 38 °C, 10 h, 88%; (c) (i) LAH, Et_2O, 0 °C to rt, 3 h, 95%; (ii) iodoacetic acid, DCC, DMAP (0.1 equiv), CH_2Cl_2, rt, 45 min, 92%; (d) Et_3B (1 M in THF, 0.1 equiv), H_2O (0.01 M in **12**), rt, 3 h, 92%; (e) DBU (2 equiv), PhMe, reflux, 2 h, 70%; (f) LiBr (3 equiv), DMF, 150 °C, 3 h, 8% of **10** and 65% of **17**.

(*R*)-cyclopent-2-ene-1-carboxylic acid obtained by Helmchen et al., $[\alpha]_D^{20}$ +260° (*c* 1.3, $CHCl_3$), via a different route, indicating a complete retention of the stereochemical integrity of the (*R*) stereocenter.[14] It should be pointed out that this approach represents a new concise and efficient method for synthesis of scalemic acid **15** in excellent yield (88%) and high enantiomeric excess (>98%). This acid, due to its simple structure, can serve as starting material for the syntheses of numerous natural products.[14] Subsequent conversion of acid **15** into cyclopentenol iodoacetate **12** was executed in two simple steps, namely via LAH reduction ($LiAlH_4$, Et_2O, 0 °C, 95%), followed by esterification with iodoacetic acid in the presence of DCC (cat. DMAP, DCM, CH_2Cl_2, room temperature (rt), 92%).

The key atom-transfer radical cyclization of α-iodoester **12** to the desired bicyclic iodolactone **11** smoothly proceeded under Oshima et al.'s conditions (Et_3B, Ar, O_2 (trace), H_2O, rt),[11] affording a 92:8 mixture of **11**-*syn* and **11**-*anti* C−I epimers in a gratifying 90% isolated yield. The main syn-stereochemistry of the product clearly indicated that the intermediate secondary C-radical resulting from the cyclization of **12** was preferentially intercepted by a radical iodine from the less hindered convex face.[15] Although the conversion of lactone **11** into olefin **10** appeared, at first sight, to be a simple task, actually it required an unexpectedly lengthy experimentation. Thus, direct elimination of hydroiodic acid from lactone **11** to form olefin **10** was unfeasible. Indeed, on exposure to DBU in refluxing toluene, the mixture of iododerivates **11** readily afforded cyclopropane lactone **16**, arising from lactone enolization, followed by intramolecular alkylation with displacement of iodine in an S_N2 fashion. Other different combinations of strong bases, solvents, and temperatures equally met with no success. We then turned our attention to a dehydrohalogenation procedure with a weak base in a dipolar aprotic solvent, such as LiBr in DMF,[16] under which conditions lactone enolization should have been minimal. In the event, the treatment of mixture of iodolactones **11** with LiBr (3 equiv, DMF, 150 °C, 3 h) afforded conjugated enone **17** in 65% isolated yield, in addition to olefin **10** in minor amounts (8% isolated yield).

SCHEME 4



Though lacking experimental proof, we speculated that formation of this enone could be explained on the basis of the main characteristics of the alkyl halides elimination reaction induced by LiBr in DMF: (i) the anti orientation of the involved halogen and hydrogen atoms, in accordance with the stereoelectronic requirements of the proposed E2C-like mechanism, (ii) the strong tendency of olefin formation to obey Saytzeff's rule, and (iii) the facile competitive S_N2 halogen substitution reaction (Scheme 4).[17]

Thus, according to our interpretation, at first **11**-*syn* and **11**-*anti* iodolactones gave a fast S_N2 iodine−bromine exchange to give bromolactones **18** and **19**, respectively, which then underwent an anti E2C elimination to afford a mixture of olefins **20** and **10**, respectively.

Basic solvent (DMF) mediated isomerization of the double bond in lactone **20** finally produced the conjugated olefin **17** as the major product. [The ^1H NMR spectrum of compound **17** was in agreement with the proposed structure: (300 MHz, $CDCl_3$) δ 5.32 (t, $J = 2$ Hz, 1H), 4.58 (dd, part A of an ABX system, 1H), 3.99 (dd, part B of an ABX system, 1H), 2.87 (br m, 1H), 2.75−2.46 (ddd, 2H), 2.05 (m, 2H), 1.81 (m, 1H), 1.25 (m, 1H).]

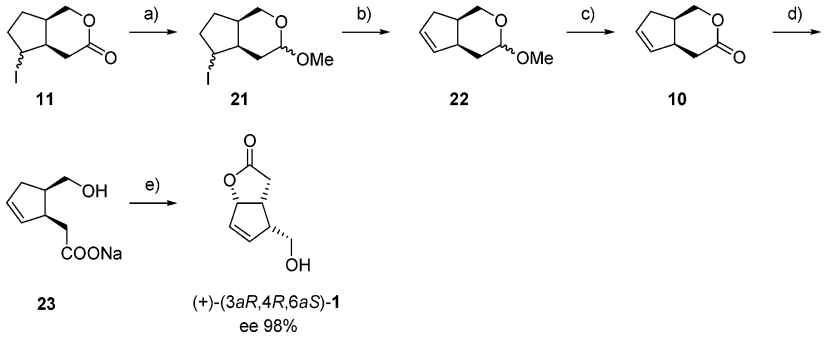
(14) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 2122.

(15) Syn and anti refer to the relative stereochemistry between iodine and 4a-H. Relative stereochemistry has been assigned through the transformation of iodolactone **11** in the cyclopropane derivatives **16**. Indeed, only the anti isomer undergoes the S_N2 reaction.

(16) Smith, M. B.; March, J. In *Advanced Organic Chemistry: Reaction, Mechanism and Structure*, 5th ed.; Wiley: New York, 2001; pp 1313−1314 and references therein.

(17) (a) Bartsch, R. A. *J. Org. Chem.* **1970**, *35*, 1023. (b) Biale, G.; Cook, D.; Lloyd, D. J.; Parker, A. J.; Stevens, I. D. R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc.* **1971**, *93*, 4735. (c) Biale, G.; Parker, A. J.; Smith, S. G.; Stevens, I. D. R.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 115. (d) Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432. (e) Gharbi-Benarous, J.; Morales-Rios, S.; Dana, G. *Can. J. Chem.* **1985**, *63*, 2384.

SCHEME 5[a]



[a] Reagents and conditions: (a) (i) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (ii) MeOH, PTSA (0.1 equiv), −20 °C, 18 h, 98% yield over two steps; (b) KHMDS, THF, −20 °C, 68 h, 95%; (c) (i) 0.3 M HCl (0.5 equiv), THF−H_2O (7:3), rt, 26 h, 98%; (ii) TPAP (5% mol), NMO (2 equiv), CH_2Cl_2, rt, 2 h, 90%; (d) NaOH (0.98 equiv), EtOH−H_2O (1:1), 80 °C, 14 h, quant; (e) $Pd(OAc)_2$ (0.05 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.05 equiv), AcOH (1.05 equiv), MeCN−MeOH (7:3), O_2 (10.1325 kPa), rt, 8 h, 99%.

These results clearly indicated that the lactone functionality had to be removed prior to iodine elimination to circumvent the problems caused by the α-carbonyl protons acidity. The mixture of lactones **11** was therefore reduced (DIBAL-H, CH_2Cl_2, −78 °C, 100%) to the corresponding lactols, which were immediately protected as methyl acetals **21** in 98% yield (Scheme 5).

With iodoacetals **21** in our hands, the synthesis of key hydroxylactone **1** proceeded quickly in a few additional steps, as outlined in Scheme 5. Elimination of hydroiodic acid with strongly hindered KHMDS at −20 °C provided the kinetically favored olefin **22**, as a mixture of methyl acetals, in a gratifying 95% yield.[18] Acid-mediated unveiling of the hemiacetal functionality (0.3 N HCl, THF−H_2O, 100%), followed by TPAP−NMO oxidation, afforded the regioisomerically pure olefin lactone **10** in 90% isolated yield. Despite being quite lengthy, the entire synthetic sequence was executed in a satisfactory 82% overall yield.

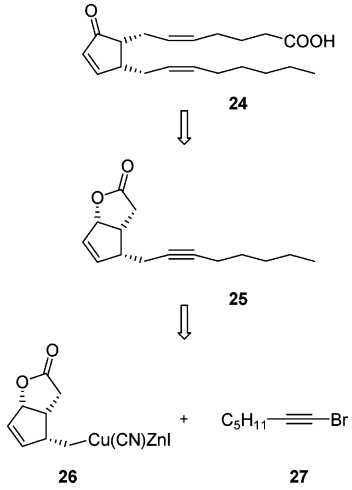
Exposure of compound **10** to NaOH in aqueous ethanol (EtOH−H_2O, 1:1, 80 °C, 100%) readily afforded the corresponding sodium carboxylate **23**, which, following our well-established protocol, underwent a smooth Pd(II)-promoted lactonization to **1** in 99% isolated yield.[9]

The (+)-(3a*R*,4*R*,6a*S*)-γ-lactone **1** was thus obtained in 75% isolated yield and with the same enantiomeric excess (98%, determined by chiral GC analysis) as the starting nitroderivative **13**, indicating an entire strikingly stereoconservative synthetic sequence.

Total Synthesis of Preclavulone A. Preclavulone-A (**24**) has been suggested to be the key intermediate in the biosynthesis of a group of marine prostanoids, named clavulones, isolated from different marine organisms such as the Okinawan soft coral *Clavularia viridis*.[19a,b] Clavulones have recently received much attention owing to their biological activities, structural features, and unique biosynthetic pathway.[19c]

The only enantioselective synthesis of (8*R*,12*R*)-preclavulone A (**24**) known thus far was described by Corey and Xiang in 1988; however, a full spectroscopic characterization was reported only for the corresponding methyl ester but not for the free acid.[20] More recently, Ito et al. published a stereoselective total synthesis of (±)-preclavulone A methyl ester and its trans-diastereomer (epipreclavulone-A methyl ester).[21] Here we illustrate an alternative straightforward asymmetric approach to preclavulone A along with its complete spectroscopic data. (It should be pointed out that the complete structural description of an intermediate is of paramount importance for biosynthetic studies.) Our synthetic strategy focused on the installation of the lower side chain via an sp^3−sp C−C coupling based on Knochel organozinc chemistry (e.g., through the coupling of the functionalized copper−zinc reagent **26** (FG-RCu(CN)ZnI) with 1-bromoalkyne **27**; Scheme 6).[22]

SCHEME 6. Retrosynthetic Analysis of Preclavulone A



In the event, the freshly prepared (3a*R*,4*R*,6a*S*)- hydroxymethyllactone **1** was readily converted to the corresponding iodide **28** via a Mitsunobu reaction with I_2 in the presence of Ph_3P (Ph_3P, imidazole, THF, rt, 85%).

The key mixed organometallic reagent **26** was then obtained from iodide **28** according to the one pot/two steps Knochel procedure, that is, through initial preparation of the organozinc intermediate **29** by Zn oxidative insertion into the C−I bond (Et_2Zn, cat. $Ni(acac)_2$, THF, −10 °C, 1.5 h), followed by transmetalation with CuCN·2LiCl in THF at 0 °C (Scheme 7).[23]

(18) Surprisingly, DBU in refluxing toluene delivered olefin **22** in only 50% yield.

(19) (a) Watanabe, K.; Sekine, M.; Iguchi, K. *Chem. Pharm. Bull.* **2003**, *51*, 909. (b) Corey, E. J.; Matsuda, S. P. T.; Nagata, R.; Cleaver, M. B. *Tetrahedron Lett.* **1988**, *29*, 2555. (c) Grechkin, A. N. *J. Lipid Mediators Cell Signalling* **1995**, *11*, 205.

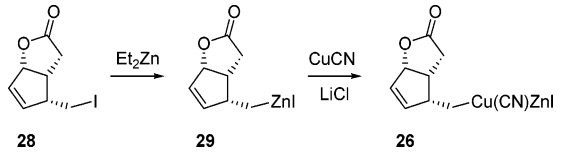
(20) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1988**, *29*, 995.

(21) Ito, H.; Konishi, M.; Iguchi, K. *Tetrahedron Lett.* **2004**, *45*, 1941.

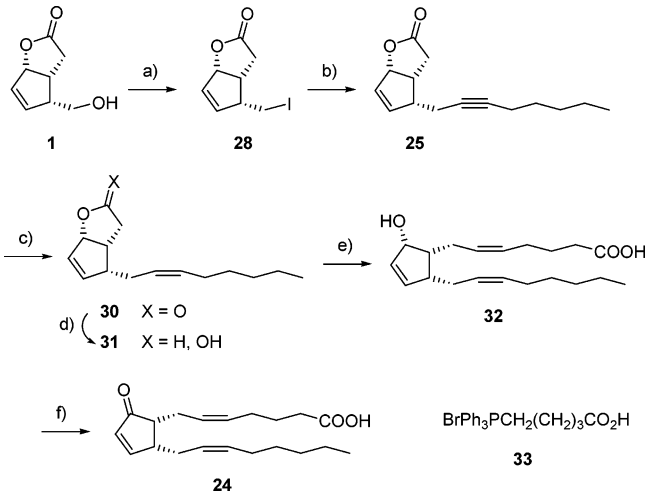
(22) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(23) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473.

SCHEME 7



SCHEME 8[a]



[a] Reagents and conditions: (a) I_2, Ph_3P, Im (2 equiv), 0 °C to rt, 85%; (b) (i) Et_2Zn (2 equiv), $Ni(acac)_2$ (0.01 equiv), THF, −10 °C, 1.5 h; (ii) CuCN (2.1 equiv), LiCl (4.2 equiv), THF, −40 to 0 °C, 5 min, −78 °C; (iii) 1-bromo-1-heptyne **27** (3.5 equiv), −78 to 50 °C, 24 h, 56%; (c) H_2 (1 atm), Lindlar (0.2 equiv), EtOAc, rt, 5 days, 94%; (d) DIBAL-H, CH_2Cl_2, −78 °C, 40 min, quant; (e) **33**, *t*-BuOK, THF, rt, 30 min, 96%; (f) Dess−Martin periodinane, CH_2Cl_2, rt, 3 h, 97%.

The copper−zinc complex **26** was then cooled to −78 °C and treated with 1-bromo-1-heptyne **27**,[24] producing the expected coupling product **25** in 57% isolated yield. With lactone **25** in hand, Lindlar chemoselective reduction of the triple bond afforded the stereochemically pure *Z* olefin **30** (H_2, 5% Pd on $CaCO_3$ poisoned with lead, EtOAc, 5 d). The upper side chain was then installed by a Wittig condensation, using the consolidated prostaglandin chemistry (Scheme 8).[25]

Thus, standard olefination of the masked aldehyde function of hemiacetal **31**, obtained by DIBAL-H reduction of lactone **30** (DIBAL-H, CH_2Cl_2, −78 °C, 99%), with the nonstabilized Wittig reagent derived from phosphonium salt **33**, smoothly gave the corresponding *Z* olefin **32** in a gratifying 96% isolated yield. Finally, Dess−Martin oxidation[26] of sensitive cyclopentenol **32** afforded synthetic preclavulone A (**24**) in 90% yield as a colorless oil, $[\alpha]_D^{20}$ −125.6° (*c* 0.18, CH_2Cl_2).

In summary, we have developed a general strategy for the enantioselective preparation of the key building block **1** for prostanoids and isoprostanes synthesis. Through a combination of state-of-the-art organometallic chemistry, that is, asymmetric allylic alkylation, and green chemistry, namely an atom-transfer radical cyclization in water, hydroxylactone **1** has been obtained in 40% overall yield and 98% ee starting from the cheap carbonate **14**. The synthetic versatility of compound **1** has been further demonstrated by the asymmetric synthesis of (−)-preclavulone A (**24**), an intriguing metabolite postulated to occur in the biosynthesis of clavulones.

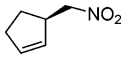
(24) Maleczka, R. E.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958.

(25) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley-Intrescience: New York, 1989; p 255.

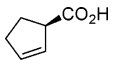
(26) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Experimental Section

(*R*)-3-(Nitromethyl)cyclopent-1-ene (13). To a solution of Trost's ligand (*S*,*S*)-**L*** (400 mg, 8% mol) in dry CH_2Cl_2 (12 mL) under an argon atmosphere was added $Pd_2dba_3{\cdot}CH_3Cl$ (203 mg, 3% mol). After 40 min, the resulting yellow solution was added to a solution of allylic carbonate **14**[12] (965 mg, 6.79 mmol), $MeNO_2$ (2.93 mL, 54.32 mmol, 8 equiv, freshly distilled from CaH_2 under argon), and BSA (1.85 mL, 7.47 mmol, 1.1 equiv) in freshly distilled dry CH_2Cl_2 (24 mL) under an argon atmosphere. The resulting mixture was stirred at rt for 1 h and evaporated under reduced pressure to give a residue that was purified by flash chromatography on silica gel. Elution with hexane−CH_2Cl_2 (8:2) gave compound **13** (800 mg, 93%, 98% ee) as a colorless oil. $[\alpha]_D^{20}$ +82° (*c* 2, CH_2Cl_2). Spectroscopic data for compound **13** were in perfect agreement with those reported in the literature.[10]



(*R*)-Cyclopent-2-enecarboxylic Acid (15). Solid $NaNO_2$ (1.73 g, 25.2 mmol, 4 equiv), followed by acetic acid (3.6 mL, 63 mmol, 10 equiv), was added to a solution of compound **13** (800 mg, 6.3 mmol) in DMSO (20 mL). The resulting mixture was heated to 40 °C and stirred for 10 h, then diluted with water (40 mL) and Et_2O (50 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with pentane−Et_2O (85:15) gave compound **15** (621 mg, 88%). $[\alpha]_D^{20}$ +260° (*c* 0.55, CH_2Cl_2). Spectroscopic data for acid **15** were in perfect agreement with those reported in the literature.[14] Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.31; H, 7.21.

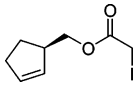


((*R*)-Cyclopent-2-enyl)methyl-2-iodoacetate (12). A solution of cyclopentene acid **15** (500 mg, 4.46 mmol) in dry Et_2O (3 mL) was added under an argon atmosphere to a suspension of $LiAlH_4$ (255 mg, 6.7 mmol, 1.5 equiv) in dry Et_2O (10 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 3 h, and then H_2O was added until complete destruction of $LiAlH_4$. The precipitate was filtered through a pad of Celite, and the resulting solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the desired alcohol (416 mg, 95%), which was directly used in the next synthetic step.

The alcohol was dissolved in dry CH_2Cl_2 (20 mL) under an argon atmosphere, and iodoacetic acid (825 mg, 1.05 equiv), DCC (963.2 mg, 1.1 equiv), and DMAP (cat.) were added to the resulting stirred solution. After 45 min, H_2O (20 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

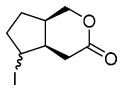
The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (96:4) gave compound **12** (1.03 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ +75.5° (*c* 3.25, CH_2Cl_2); IR (liquid film): ν(tilde) 2958, 1739, 1429, 1388, 1244, 1169, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.66 (m, 1H), 4.07 (dd, J = 1.4, 1.7 Hz, 2H), 3.70 (s, 2H), 3.04 (m, 1H), 2.37 (m, 2H), 2.05 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 s, 133.7 d, 130.8 d, 69.7 t, 45.3 d, 32.3 t, 26.8 t, −0.5 t; EIMS (70 eV) *m*/*z* 169 $(ICH_2CO)^+$, 141 $(ICH_2)^+$, 127 $(I)^+$, 80 (M

$-$ OCOCH$_2$I)$^+$, 67 (M $-$ CH$_2$OCO)$^+$. HRMS calcd for $C_8H_{11}IO_2$, 265.9804; found, 265.9811.



(4a*R*,7a*R*)-Hexahydro-5-iodocyclopenta[*c*]pyran-3(1*H*)-one (11). Et$_3$B (0.365 mL, 1 M solution in THF, 0.1 equiv) was added dropwise to a suspension of iodoacetate **12** (0.83 g, 3.65 mmol) in H_2O (365 mL) under an argon atmosphere obtained with the use of a toy balloon, and the resulting mixture was stirred for 3 h. The solution was then saturated with NaCl and extracted with EtOAc (4 $\times$ 200 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

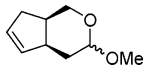
The resulting residue was purified by flash chromatography on silica gel. Elution with hexane$-$Et$_2$O (1:1) gave compound **11** (0.76 g, 92%) as a 98:2 mixture of *syn*/*anti* 5-iodo epimers (GC analysis). IR (liquid film): ν(tilde) 2958, 1736, 1426, 1388, 1242, 1171, 1090, 1039, 945 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.14 (dd, J = 11.6, 4.6 Hz, 1H), 3.94 (dd, J = 11.6, 5.5 Hz, 1H), 3.55 (ddd, J = 15.3, 8.5, 5.7 Hz, 1H), 2.68 (m, 1H), 2.57 (dd, J = 15.3, 6.8 Hz, 1H), 2.48 (m, 1H), 2.32 (dd, J = 15.3, 5.7 Hz, 1H), 2.10 (m, 1H), 1.88 (m, 2H), 1.31 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.0 s, 69.3 t, 46.7 d, 39.5 t, 36.2 d, 32.7 t, 29.0 d, 28.8 t; EIMS (70 eV) *m*/*z* 267 (M + 1)$^+$, 139 (M $-$ 1)$^+$, 121 (M $-$ I $-$ H$_2$O)$^+$, 95 (M $-$ I $-$ CO$_2$)$^+$, 81 (M $-$ I $-$ CH$_2$CO$_2$)$^+$, 67 (C$_5$H$_7$)$^+$. HRMS calcd for $C_8H_{11}IO_2$, 265.9804; found, 265.9798.



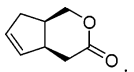
(4a*R*,7a*R*)-Octahydro-5-iodo-3-methoxycyclopenta[*c*]pyran (21). DIBAl-H (5.3 mL, 1 M solution in hexane, 1.3 equiv) was added dropwise to a solution of lactone **11** (1.1 g, 4.1 mmol) in dry CH$_2$Cl$_2$ (70 mL) at $-$78 °C under an argon atmosphere. After the resulting solution had been stirred for 30 min, excess hydride was destroyed by adding a saturated solution of NH_4Cl (100 mL). CH$_2$Cl$_2$ (100 mL) was then added, the resulting mixture was warmed to rt, and 6 N HCl was added until the two phases were completely separated. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 $\times$ 40 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

The resulting residue was dissolved in MeOH (50 mL) and cooled to $-$20 °C, and then PTSA (cat.) was added. After 18 h, excess solid $NaHCO_3$ was added, and the resulting mixture was stirred for 15 min and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and a saturated solution of $NaHCO_3$ (50 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane$-$EtOAc (95:5) gave compound **21** (1.13 g, 98%) as a 1:1 mixture of anomers. IR (liquid film): ν(tilde) 2956, 1428, 1391, 1240, 1169, 1091, 1037, 949 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.6 (m, 1H), 4.55 (m, 1H), 3.9$-$4.4 (m, 2H), 3.5 (m, 1H), 3.37 (s, 3H), 2.1$-$2.6 (m, 3H), 1.6$-$2.1 (m, 3H), 1.35 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 98.6 and 97.5 d (each value refers to each of the anomers), 61.2 and 61.0 t, 54.8 and 54.6 q, 47.3 and 45.5 d, 37.3 and 37.2 t, 35.5 and 35.0 d, 32.0 and 31.7 d, 29.5 and 29.2 t, 25.9 and 25.8 t; EIMS (70 eV): *m*/*z* (%) 282 (M)$^+$ (2), 251 (M $-$ OMe)$^+$ (10), 123 (86), 105 (20), 95 (100), 79 (70), 67 (90), 55 (6). HRMS calcd for $C_9H_{15}IO_2$, 282.0117; found, 282.0120.

(4a*S*,7a*R*)-1,3,4,4a,7,7a-Hexahydro-3-methoxycyclopenta[*c*]-pyran (22). KHMDS (7.6 mL, 0.5 M solution in toluene, 1.65 equiv) was added dropwise to a solution of iodide **21** (612 mg, 2.17 mmol) in dry THF (12 mL) cooled to $-$78 °C under an argon atmosphere. The temperature was allowed to rise to $-$20 °C and then kept at this value for 68 h. The formation of a white flocculent precipitate was observed. The solution was diluted with Et$_2$O (100 mL), and H_2O (20 mL) was added. The layers were separated, and the aqueous phase was extracted with Et$_2$O (4 $\times$ 20 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure (P > 200 mmHg). The resulting residue was purified by flash chromatography on silica gel. Elution with pentane$-$Et$_2$O (from 99.5:0.5 to 95:5) gave compound **22** (320 mg, 95%) as a colorless oil. IR (liquid film): ν(tilde) 2957, 2928, 2859, 1444, 1196, 1037 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.70 (m, 2H), 4.55 (m, 1H), 3.6$-$4.0 (m, 2H), 3.4 (s, 3H), 2.7$-$3.0 (m, 1H), 2.25$-$2.5 (m, 2H), 1.6$-$2.1 (m, 2H), 1.45 (ddd, J = 13.9, 9.5, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 134.6 and 134.5 d (each value refers to each of the anomers), 130.5 and 129.7 d, 99.5 and 98.8 d, 63.4 and 62.4 t, 55.14 q, 40.0 and 39.0 d, 35.8 and 35.24 d, 35.5 and 34.4 t, 31.9 and 31.6 t; EIMS (70 eV): *m*/*z* (%) 154 (M)$^+$ (5), 123 (M $-$ OMe)$^+$ (25), 91 (20), 79 (100), 66 (55), 39 (28). HRMS calcd for $C_9H_{14}O_2$, 154.0994; found, 154.0988.

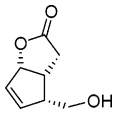


(4a*S*,7a*R*)-4,4a,7,7a-Tetrahydrocyclopenta[*c*]pyran-3(1*H*)-one (10). HCl (0.3 N, 1.66 mL) was added to a solution of methylacetal **22** (320 mg, 2.07 mmol) in THF$-$H$_2$O 7:3 (26 mL), and the resulting mixture was stirred for 26 h. More HCl (0.3 N, 0.34 mL) was added, and after four additional hours the acidity was quenched by the addition of excess solid $NaHCO_3$. The resulting mixture was diluted with CH_2Cl_2 (30 mL), and a phosphate buffer (10 mL, pH = 6.95) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic phases were washed with H_2O (10 mL) and brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane$-$EtOAc (85:15) gave the desired lactol (288 mg, 98%), which was immediately dissolved in dry CH_2Cl_2 (28.8 mL) under an argon atmosphere. Molecular sieves (4 Å, 10 mg) were added, followed by NMO (482 mg, 2 equiv) and cat. TPAP. The resulting mixture was stirred for 2 h, then filtered through a pad of Celite, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane$-$EtOAc (8:2) gave compound **10** (252 mg, 90%). Spectroscopic data for compound **10**, $[\alpha]^{20}_D$ +77.84° (*c* 1.25, CH_2Cl_2), were in perfect agreement with those reported in the literature.[5] HRMS calcd for $C_8H_{10}O_2$, 138.0681; found, 138.0677.

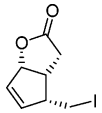


(3a*R*,4*R*,6a*S*)-4-(Hydroxymethyl)-3a,4-dihydro-3*H*-cyclopenta[*b*]furan-2(6a*H*)-one (1). Olefin **10** (890 mg, 6.45 mmol) was dissolved in a EtOH$-$H$_2$O (1:1) mixture (15 mL), and solid NaOH (253 mg, 6.32 mmol) was added. The solution was stirred for 14 h at 80 °C. After cooling, the solvent was removed under vacuum and the residual water was removed by azeotropical distillation using MeCN (3 $\times$ 100 mL). The light beige solid thus obtained was washed with ether, and the suspension was filtered through a sintered glass funnel. Olefin salt **23** was thus obtained as a white solid (1.145 g, almost quantitative).

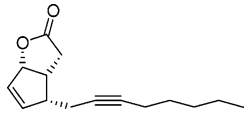
In a three-neck round-bottom flask, equipped with a gas-inlet system, a double surface condenser, and a silicon septum, the sodium salt **23** (1.448 g, 2.5 mmol) was dissolved in MeOH (4.3 mL). MeCN (2.8 mL) and AcOH (150 μL, 1.05 equiv) were then added with stirring, while O_2 was bubbled in the reaction mixture (3 mL min^{-1}). The heterobimetallic couple was then prepared by dissolving $Pd(OAc)_2$ (28 mg, 0.125 mmol) and $Cu(OAc)_2 \cdot H_2O$ (25 mg, 0.125 mmol) in MeCN (2 mL). The emerald solution thus obtained was stirred under oxygen for 15 min, and then added via cannula to the substrate solution. The resulting mixture was stirred under a stream of O_2 for 18 h. Solvents were evaporated under vacuum, and the brown residue was taken up with AcOEt and filtered. The organic phase was washed with brine and dried over $MgSO_4$. Rotary evaporation of the volatiles left a crude residue as a yellow oil that was purified by flash chromatography on silica. Elution with hexane−EtOAc (1:1) gave lactone **1** as a colorless oil (381 mg, 99%), $[\alpha]_D^{20}$ +4.68° (*c* 0.775, CH_2Cl_2). Spectroscopic data for compound **1** were in perfect agreement with those reported in the literature.[9]



(3a*R*,4*R*,6a*S*)-3a,4-Dihydro-4-(iodomethyl)-3*H*-cyclopenta[*b*]-furan-2(6a*H*)-one (28). Imidazole (145 mg, 2.13 mmol, 1.05 equiv), followed by PPh_3 (693 mg, 2.64 mmol, 1.3 equiv), was added to a solution of lactone **1** (313 mg, 2.03 mmol) in dry THF (5 mL) under an argon atmosphere. The resulting mixture was stirred and cooled to 0 °C, and then I_2 (620 mg, 2.44 mmol, 1.3 equiv) was added in 30 min. The formation of a precipitate was observed while the temperature rose to room temperature. After 4 h, excess I_2 was destroyed by the addition of a saturated solution of $Na_2S_2O_3$ (7 mL), and the mixture was diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure without warming. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (9:1) gave the desired iodide **28** (452 mg, 85%), $[\alpha]_D^{20}$ +99.2° (*c* 1.7, CH_2Cl_2), as a pale yellow oil. IR (liquid film): ν(tilde) 2955, 1763, 1368, 1324, 1264, 1164, 936, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (dt, J = 6.5, 2 Hz, 1H), 5.96 (dt, J = 6.5, 3 Hz, 1H), 5.47 (br d, J = 8 Hz, 1H), 3.34 (m, 3H), 3.01 (m, 1H), 2.67 (dd, J = 18, 10 Hz, 1H), 2.49 (dd, J = 18, 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1 s, 137.7 d, 130.4 d, 87.8 d, 49.1 d, 40.4 t, 28.4 d, 3.6 t; EIMS (70 eV): *m*/*z* (%) 264 $(M)^+$ (4), 149 (6), 138 (10), 137 (100), 119 (20), 91 (41), 81 (48). HRMS calcd for $C_8H_9IO_2$, 263.9647; found, 263.9651.



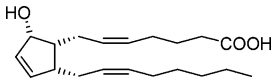
(3a*R*,4*R*,6a*S*)-3a,4-Dihydro-4-(oct-2-ynyl)-3*H*-cyclopenta[*b*]furan-2(6a*H*)-one (25). $Ni(acac)_2$ (10 mg) was added to a solution of iodide **28** (160 mg, 0.606 mmol) in dry THF (4 mL) under an atmosphere of argon. The mixture was stirred and cooled to −10 °C, and Et_2Zn (1 M solution in hexane, 1.21 mL, 2 equiv) was added. After 1.5 h, the resulting mixture was cooled to −40 °C, and a solution of CuCN (114 mg, 1.27 mmol, 2.1 equiv) and LiCl (109 mg, 2.54 mmol, 4.2 equiv) in dry THF (3 mL) was added. The temperature was allowed to rise to 0 °C and, after 5 min, brought to −78 °C. Neat 1-bromo-1-heptyne **27** (0.277 mL, 3.5 equiv) was then added dropwise, and the temperature was allowed to rise to −50 °C. After 24 h, a buffer of NH_4Cl-NH_3 (10 mL, pH = 8) was added, and the resulting mixture was warmed to room temperature and diluted with Et_2O (23 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 14 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure without warming. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (from 99:1 to 96:4) gave the desired alkyne **25** (78.4 mg, 56%), $[\alpha]_D^{20}$ +32.3° (*c* 0.47, CH_2Cl_2), as a pale yellow oil. IR (liquid film): ν(tilde) 2955, 2923, 2853, 1770, 1448, 1192, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.9−6.0 (m, 2H), 5.48 (dd, J = 7.4, 0.8 Hz, 1H), 3.3 (quintet, J = 8.6 Hz, 1H), 3.1 (dd, J = 14.2, 8 Hz, 1H), 2.5−2.6 (d, J = 14.2 Hz, 2H), 2.3 (m, 2H), 2.15 (m, 2H), 1.5 (m, 2H), 1.4 (m, 4H), 0.9 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0 s, 139.1 d, 129.0 d, 88.5 d, 82.5 s, 76.8 s, 46.0 d, 39.0 d, 31.0 t, 29.2 t, 28.4 t, 22.0 t, 20.6 t, 18.5 t, 13.9 q; EIMS (70 eV): *m*/*z* (%) 232 $(M)^+$ (5), 173 (10), 157 (15), 144 (20), 130 (50), 117 (30), 91 (50), 79 (100), 67 (60), 53 (55), 41 (80). HRMS calcd for $C_{15}H_{20}O_2$, 232.1463; found, 232.1459.



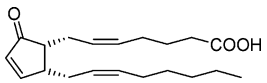
(3a*R*,4*R*,6a*S*)-3a,4-Dihydro-4-((*Z*)-oct-2-enyl)-3*H*-cyclopenta-[*b*]furan-2(6a*H*)-one (30). Lindlar catalyst (20 mg) was added to a solution of alkyne **25** (110 mg, 0.47 mmol) in EtOAc (9 mL). A static atmosphere of H_2 was created, and the mixture was stirred for 5 d. The mixture was then filtered and concentrated under reduced pressure to yield alkene **30** (19 mg, 94%), $[\alpha]_D^{20}$ +33.7° (*c* 1, CH_2Cl_2), as a pale yellow oil. IR (liquid film): ν(tilde) 2956, 2924, 2853, 1771, 1447, 1199, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 5.9−6.0 (m, 2H), 5.5 (dd, J = 4.0, 1.0 Hz, 2H), 5.3 (m, 1H), 3.25 (quintet, J = 7.14 Hz, 1H), 2.95 (m, 1H), 2.25 (d, J = 9 Hz, 2H), 2.1−2.3 (m, 2H), 2.0 (dd, J = 13.9, 7.14 Hz, 2H), 1.1 (m, 6H), 0.98 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0 s, 139.7 d, 132.1 d, 128.3 d, 126.0 d, 88.9 d, 46.5 d, 39.5 d, 31.4 t, 29.3 t, 29.1 t, 28.7 t, 27.4 t, 22.4 t, 13.9 q; EIMS (70 eV): *m*/*z* (%) 234 $(M)^+$ (5), 191 (12), 174 (12), 132 (25), 124 (30), 117 (22), 96 (30), 79 (70), 78 (100), 67 (50), 65 (16). HRMS calcd for $C_{15}H_{22}O_2$, 234.162; found, 234.1616.

(5*Z*)-7-((1*R*,2*S*,5*R*)-2-Hydroxy-5-((*Z*)-oct-2-enyl)cyclopent-3-enyl)hept-5-enoic Acid (32). DIBAl-H (1 M solution in hexane, 244 μL, 1.3 equiv) was added to a solution of lactone **30** (44 mg, 0.188 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C under an argon atmosphere. The resulting mixture was stirred for 1 h, and then excess hydride was destroyed by adding a saturated solution of NH_4Cl (10 mL). CH_2Cl_2 (15 mL) was added, the resulting mixture was warmed to room temperature, and 6 N HCl was added until complete separation of the two phases. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 4 mL). The combined organic phases were washed with H_2O, followed by brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (8:2) gave the desired lactol **31** (42 mg, 100%), which was used immediately in the next step. *t*-BuOK (160 mg, 1.42 mmol, 8 equiv) was added to a stirred suspension of carboxybutyltriphenylphosphonium bromide **33** (316 mg, 0.712 mmol, 4 equiv) in dry THF (2.5 mL) at room temperature. The mixture was allowed to react for 30 min. Afterward, to the resulting red suspension of the ylide, crude lactol **31** (42 mg, approximately 0.178 mmol) in THF (1.8 mL) was added via cannula. The mixture was stirred for 2 h and

quenched by the successive addition of a saturated solution of NH_4Cl (15 mL) and AcOH (0.084 mL, 8.4 equiv). The suspension was diluted with Et_2O (10 mL), and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (8:2) delivered compound **32** (55 mg, 96%), $[\alpha]_D^{20}$ −32.3° (*c* 0.6, CH_2Cl_2), as a colorless oil. IR (liquid film): ν(tilde) 3416, 2926, 1708, 1406, 1240, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.14 (dd, J = 5.7, 2.6 Hz, 1H), 5.97 (m, 1H), 5.25−5.6 (m, 4H), 4.5 (dd, J = 5.8, 2.6 Hz, 1H), 1.6 (m, 1H), 2.0−2.5 (m, 11H), 1.75 (quintet, J = 7.5 Hz, 2H), 1.3 (m, 8H), 0.9 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9 s, 140.9 d, 131.9 d, 131.3 d, 126.6 d, 129.0 d, 127.4 d, 76.2 d, 46.2 d, 45.5 d, 33.2 t, 31.3 t, 30.0 t, 28.2 t, 27.2 t, 26.5 t, 24.3 t, 23.0 t, 2.3 t, 13.8 q; ESI-MS (APCI): *m*/*z* 303 $[M + 1 - H_2O]^+$. HRMS calcd for $C_{20}H_{32}O_3$, 320.2351; found, 320.2354.



Preclavulone A (24). Dess−Martin periodinane (63 mg, 0.148 mmol, 1.4 equiv) was added to a stirred solution of alcohol **32** (34 mg, 0.106 mmol) in dry CH_2Cl_2 (3 mL) under an argon atmosphere. After 3 h, Et_2O (10 mL) was added, and the resulting mixture was filtered through a pad of Celite. The solution was then concentrated under reduced pressure without warming. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc (8:2) delivered compound **24** (32 mg, 97%), $[\alpha]_D^{20}$ −125.6° (*c* 0.176, CH_2Cl_2), as a pale yellow oil. IR (liquid film): ν(tilde) 3600−3100 (CO*OH*), 2930, 1708, 1585, 1198, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$,): δ 7.7 (dd, J = 5.7, 2.7 Hz, 1H), 6.2 (dd, J = 5.7, 1.8 Hz, 1H), 5.5 (m, 4H), 3.1 (m, 1H), 2.45−2.55 (m, 3H), 2.38 (t, J = 7.5 Hz, 2H), 1.9−2.3 (m, 4H), 1.75 (quintet, J = 7.5 Hz, 2H), 1.3 (m, 8H), 0.9 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208 s, 178.6 s, 165.1 d, 132.0 d, 131.6 d, 129.3 d, 128.7 d, 126.0 d, 48.6 d, 43.6 d, 32.7 t, 31.1 t, 28.8 t, 28.1 t, 27.0 t, 26.2 t, 23.9 t, 23.6 t, 22.2 t, 13.6 q; ESI-MS (APCI): *m*/*z* 319 $[M + 1]^+$, 301.2 $[M + 1 - H_2O]^+$. HRMS calcd for $C_{20}H_{30}O_3$, 318.2195; found, 318.23.



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Supporting Information Available: ^1H, ^{13}C NMR, and DEPT spectra of compounds **11**, **12**, **21**, **22**, **24**, **25**, **28**, **30**, and **32**. ^1H NMR for compounds **10** and **15** and ^{13}C NMR for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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