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Enantioselective Synthesis of Myrtucommulone A

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Dedicated to Professor Dr. Theophil Eicher on the occasion of his 80th birthday

Keywords: Total synthesis / Asymmetric synthesis / Michael addition / Steric hindrance / Enantioselectivity

Myrtucommulone A (**1**), which was isolated from myrtle and other species of the myrtaceae family, was synthesized through an enantioselective Michael addition of isobutyryl phloroglucinol (**5**) to isobutylidene syncarpic acid (**4**) that was induced by a chiral Al–Li–BINOL (1,1′-bi-2-naphthol) complex [(*S*,*S*)-ALB]. Because there is significant steric crowding in Michael acceptor **4**, myrtucommulone A (**1**) was obtained with an *ee* value of 70 % along with *meso*-**1** in 77 % chemical yield.

Introduction

In 1974, Kashman et al.[1] reported the isolation, structure elucidation, and antibacterial activity of myrtucommulone A (**1**, MC A) and myrtucommulone B (**2**, MC B, see Figure 1) from *Myrtus communis* L. (myrtle). Later, MC A (**1**) was also found in other species of the myrtaceae family.[2–4]

We became interested in the myrtucommulones because of their anti-inflammatory[5] and cytotoxic[6] activities and developed a short and efficient synthesis for MC A (**1**) and other members of this compound family.[7] Interestingly, the synthetic MC A (**1**), which was a mixture of three stereoisomers, showed the same pharmacological activity as natural MC A (**1**) with respect to mPGES1-inhibition and induction of apoptosis.[7] This posed the question as to the stereoisomeric composition of MC A (**1**) that was isolated from *Myrtus communis*. After rigorous purification of natural MC A (**1**), we could show through its derivatization, CD spectroscopy, and enantiomeric analysis that it was also a mixture of three stereoisomers.[8] In this regard, it became important to investigate whether MC A (**1**) racemized during our derivatization reaction. Additionally, it is of interest to determine the pharmacological activities of each stereoisomer. To answer both questions, we developed an enantioselective synthesis of MC A (**1**). Herein, we wish to report our results obtained towards this end.

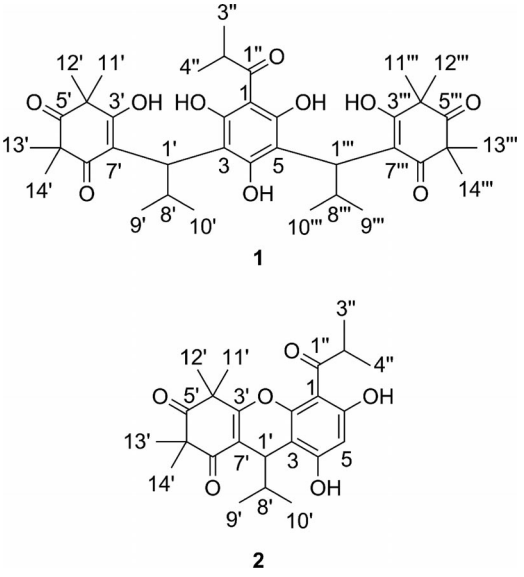

Figure 1. Structures of MC A (**1**) and MC B (**2**).

Results and Discussion

Our racemic synthesis[7] started from syncarpic acid (**3**)[9] and led to MC A (**1**) as a mixture of three stereoisomers (i.e., two enantiomers and one *meso* compound) through the reaction between isobutylidene syncarpic acid (**4**)[10] and double deprotonated isobutyryl phloroglucinol (**5**)[11] (see Scheme 1).

We could also carry out a Michael addition of deprotonated isobutyryl-phloroglucinol (**5**) to isobutylidene syn-

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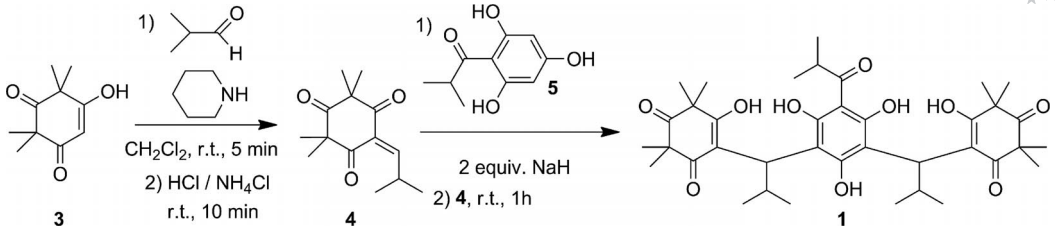
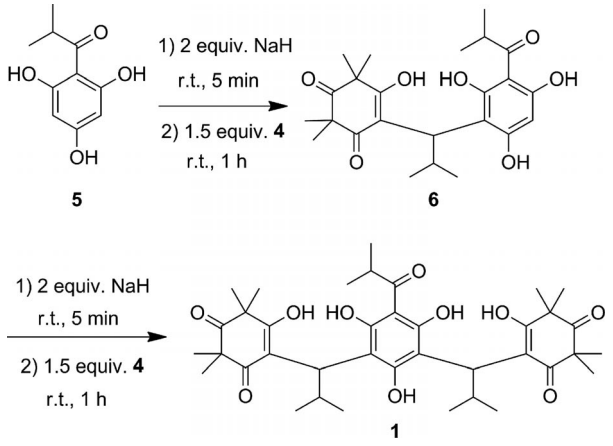


Scheme 1. Synthesis of MC A (**1**) as a mixture of three stereoisomers.

carpic acid (**4**) over two steps through nor-semimyrtucommulone (**6**, NSMC) to give MC A (**1**, see Scheme 2).



Scheme 2. Two-step synthesis of MC A (**1**) through NSMC (**6**).

For our enantioselective synthesis of MC A (**1**), we adapted this two-step procedure. It can be considered a double Michael addition of phloroglucinol derivative **5** to sterically hindered isobutylidene syncarpic acid (**4**) or a two-fold Friedel–Crafts alkylation of **5** with two molecules of **4**. Although enantioselective Michael additions[12] as well as enantioselective Friedel–Crafts alkylations[13] have been intensively studied, the existing methods[12,13] give only poor yields and/or poor enantioselectivities if the Michael acceptor (or alkylating agent) is significantly sterically hindered as is the case with **4**. Therefore, we searched for chiral reagents to transfer chirality to the less sterically hindered phloroglucinol core of **5** by using a simple acid-base reaction and a chiral reagent to substitute for NaH. After examining several chiral amines[14] without success, we switched to the well-known 1,1′-bi-2-naphthol (BINOL) reagent, lithium 2,2′-dihydroxy-1,1′-binaphthylethoxyaluminum hydride [BINALH, (*S*)-**7**] for the synthesis of **6** (see Figure 2 and Scheme 3). It was Noyori et al.[15] who developed this BINOL reagent [synthesized from (*S*)-BINOL, $LiAlH_4$, and ethanol]. Pedro et al.[16] and Reisman et al.[17] previously used modified BINOL–Zr complexes for enantioselective Friedel–Crafts alkylations of indoles with α,β-unsaturated ketones.

Using 1–6 equiv. of (*S*)-**7** with respect to **5** gave (–)-**6** with *ee* values in a range from 5 to 34%. After the cyclization to (+)-**2**, the *ee* value was determined by using HPLC analysis with a ChiralCel OD-H column (see Table 1).[18] As the cyclization reaction was carried out under the same conditions as those used for the NSMC (**6**) that was isolated from myrtle,[8] this result demonstrates that **6** does not racemize during the cyclization to **2**.

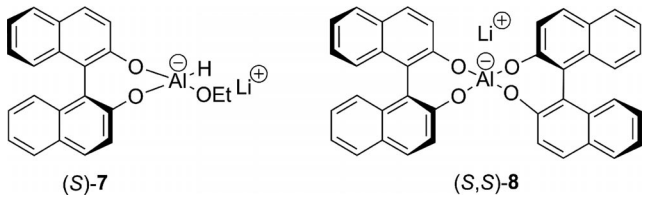
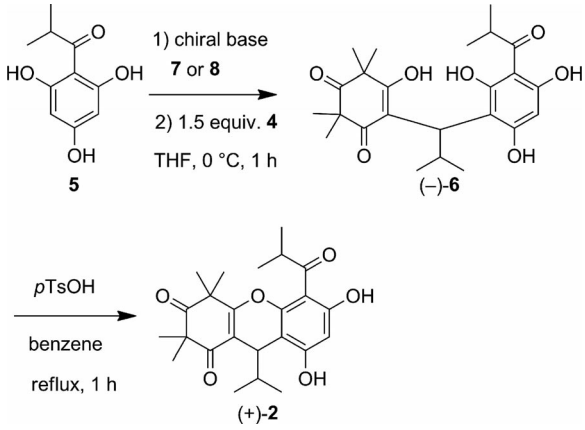


Figure 2. Chiral aluminium reagents used for enantioselective syntheses of **6** and **1**.



Scheme 3. Enantioselective synthesis of NSMC (–)-**6** with chiral bases and cyclization to (+)-**2** (for enantiomeric analysis by HPLC). Because we do not yet know the absolute configuration of the stereocenters in (–)-**6** and (+)-**2**, we did not provide the orientation of the isopropyl groups in the structures.

Table 1. Results of the reactions presented in Scheme 3.[a]

Entry	Catalyst [equiv.]	% Yield **6**[b]	% *ee* **2**[c]	$[\alpha]_D^{20}$ of (+)-**2**[d]
1	(*S*)-**7** (1)	47	5	+15
2	(*S*)-**7** (2)	70	11	+26
3	(*S*)-**7** (3)	77	23	+37
4	(*S*)-**7** (4)	64	28	+44
5	(*S*)-**7** (6)	64	34	+54
6	(*S*,*S*)-**8** (1)	69	4	–
7	(*S*,*S*)-**8** (2)	76	41	+70
8	(*S*,*S*)-**8** (3)	77	62	+105

[a] Ratio of equiv. **4**/**5** is 1.5:1, T = 0 °C. [b] Yield refers to isolated and purified substance. [c] The *ee* value was determined after cyclization to (+)-**2** by using HPLC analysis with a ChiralCel OD-H column (*i*PrOH/*n*-hexane, 30:70, 0.5 mL/min, 15 °C). The value is equal to the *ee* value of **6**. [d] Optical rotation of the mixture of enantiomers with the corresponding *ee* value.

To improve the enantioselectivity of this reaction, we used Shibasaki's Al–Li–BINOL complex[19] (**8**, ALB), which was obtained from $LiAlH_4$ and 2 equiv. of (*S*)- or (*R*)-BINOL. Carrying out the reaction of **4** with **5** in the presence of 1 to 3 equiv. of (*S*,*S*)-**8** gave (–)-**6** with *ee* values in the range from 4 to 62% [determined after cyclization to (+)-**2**, see Table 1 and Figure 3]. In the presence of 3 equiv. of (*R*,*R*)-**8**, (+)-**6** was obtained in 77% yield with 62% *ee*.

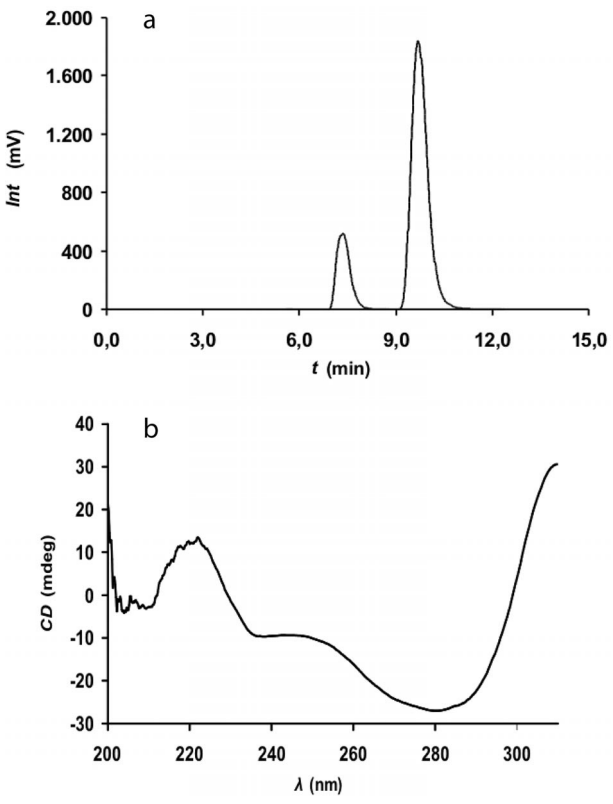
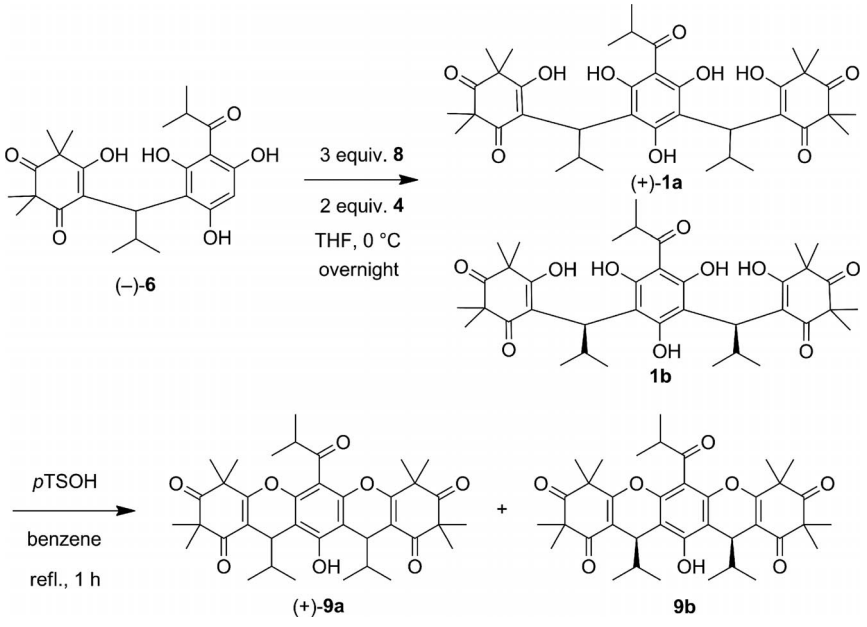


Figure 3. (a) HPLC chromatogram of (+)-**2** with 62% *ee* (ChiralCel OD-H, *i*PrOH/*n*-hexane, 30:70, 0.5 mL/min, 15 °C), (b) corresponding CD spectrum (0.1 mg/mL, MeOH, 20 °C).

Interestingly, the ^1H NMR spectrum of (+)-**2** in [D_6]acetone is identical to the ^1H NMR spectrum of the racemate, whereas in $CDCl_3$, we observed two sets of data (see Supporting Information). The ratio of the integrals from these two sets of data is 85:15, that is, the *ee* value can be determined from the ^1H NMR spectroscopic data (chiral self-discrimination).[20]

Next, we focused on the second Michael addition of (–)-**6** with an additional 2 equiv. of **4** to give MC A (**1**). We first used (*S*,*S*)-**8** in an analogous manner as in the first Michael addition. When we used 3 equiv. of (*S*,*S*)-**8**, we obtained chiral MC A (+)-**1a** with 55% *ee* and *meso* MC A (**1b**) in a ratio of almost 1:1 (chemical yield 62%). If we used 3 equiv. of (*R*,*R*)-**8**, the enantioselectivity and diastereoselectivity were improved. Chiral MC A (+)-**1a** was now obtained with an *ee* of 70%, but *meso* MC A (**1b**) was still present. The chiral product and the *meso* form were produced in a ratio of 59:41 with a combined chemical yield of 77%. Because we are not yet able to separate chiral MC A from its *meso* form, we always carried out the cyclization reaction of the mixture to give pentacyclic derivatives (PMCA) **9a** and **9b**, which could be analyzed by HPLC (see Scheme 4). Here also, racemization did not occur under the cyclization reaction conditions.T

Compounds **9a** and **9b** were separated with a preparative RP18-HPLC column (MeOH/MeCN, 80:20). Compound (+)-**9a** was analyzed with a ChiralCel OD-H column (*i*PrOH/*n*-hexane, 30:70) to determine the *ee* value (see Figure 4). he *ee* value was also determined from the ^1H NMR spectroscopic data of (+)-**9a** in $CDCl_3$.[20]



Scheme 4. Enantioselective synthesis of MC A (**1**) and the cyclization to **9**. Because we do not yet know the absolute configuration of the stereocenters of (+)-**1a** and (+)-**9a**, we did not give the orientation of the isopropyl groups in the structures.

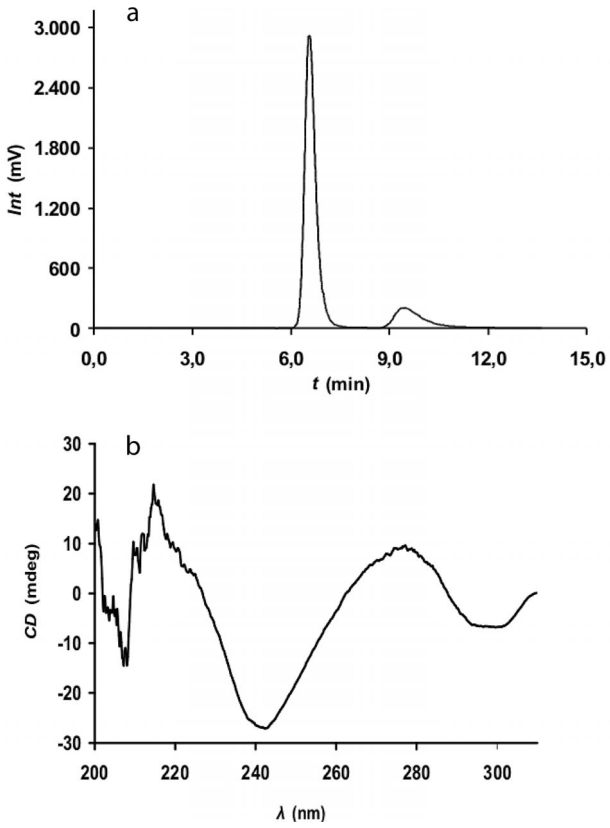
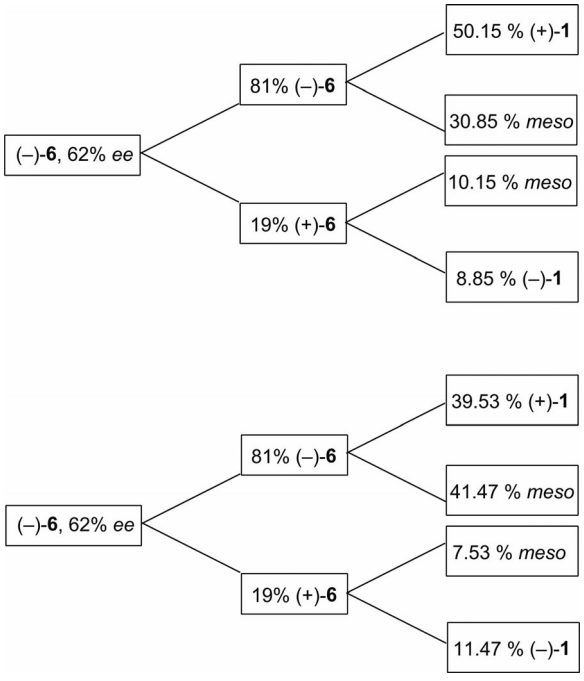


Figure 4. (a) HPLC chromatogram of **9a** with 70%*ee* (ChiralCel OD-H, *i*PrOH/*n*-hexane, 30:70, 0.5 mL/min, 15 °C): t_R = 6.56 min [for (+)-**9a**] and 8.66 min [for (–)-**9a**], (b) corresponding CD spectrum (0.1 mg/mL, MeOH, 20 °C) of (+)-**9a** with 70%*ee*.



Scheme 5. Results of the matched (a) and the mismatched (b) double-diastereodifferentiating second Michael addition from (–)-**6** to (+)-**1a**.

Both of the reactions of (–)-**6** with either (*S*,*S*)-**8** or (*R*,*R*)-**8** are typical for double-diastereodifferentiating reactions, as explained in Scheme 5.

At first sight, 70%*ee* seems to be only a moderate value, but in comparison to published methods for enantioselective Michael additions and enantioselective Friedel–Crafts alkylations, 70%*ee* is a relatively good result for significantly sterically hindered substrates like **4**. In systems that have a Michael acceptor with similar steric crowding, either the *ee* value is comparable to our result and the chemical yield is rather low[21] or the chemical yield is a moderate value and the *ee* value is zero.[22] Even under high pressure,[23] the *ee* values are comparable to our results. Unfortunately, we had to use the BINOL complexes in excess amounts because the uncatalyzed background reaction was as fast as the reaction modified by (*S*)-**7** or (*S*,*S*)-**8**. In this regard, we isolated the BINOL after workup so that it could be used one more time without any difficulty.

Conclusions

In summary, we developed enantioselective syntheses of nor-semimyrtucommulone (**6**) with 62%*ee* and myrtucommulone A (**1**) with 70%*ee*, which started from achiral isobutylidene syncarpic acid (**4**), isobutyryl phloroglucinol (**5**), and ALB (**8**) as the chiral reagent. Additionally, we showed that **6** and **1** did not racemize during the acid-catalyzed cyclizations to **2** and **9**, respectively. Current research is directed towards the elucidation of the absolute configurations of the stereogenic centers and the separation of the enantiomers of **6** and the stereoisomers of **1** without the preparation of any derivatives.

Experimental Section

General Methods: All solvents were from Merck, Darmstadt in HPLC grade. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under N_2. $LiAlH_4$ and (*R*)- and (*S*)-BINOL were purchased from Aldrich, Steinheim, Germany. All reactions were carried out in dried flasks under N_2. Optical rotations were measured in MeOH or $CHCl_3$ at 20 °C using a Perkin–Elmer 241 polarimeter with a sodium lamp. CD spectra were recorded in HPLC grade MeOH with a Jasco spectropolarimeter J-715. The NMR spectroscopic data [1D: ^1H and ^{13}C NMR, DEPT 135; 2D: H,H-COSY, heteronuclear single quantum correlation (HSQC), HMBC, NOESY] were recorded with a Bruker AVANCE II 400 (^1H NMR at 400 MHz, ^{13}C NMR at 100 MHz). Chemical shifts are given in ppm, and coupling constants are in Hz. MestReC 4.9.9.6 was used to process the NMR spectroscopic data. MS (ESI) were measured with a Shimadzu LC-MS 2020 (Shimadzu Germany, Duisburg). HRMS (ESI) were measured with a LTQ Orbitrap XL from Thermo Scientific, Dreieich, Germany. TLC was performed on silica glass plates (Si60 F_{254} from Merck) and RP18 silica glass plates (RP18-F_{254} from Merck). Flash chromatography was carried out by using silica gel with 40–63 μm particle size from Merck. Analytical HPLC was performed with a SYKAM HPLC instrument (SYKAM, Fürstenfeldbruck, Germany, gradient pump S3100, mixer S8111, DAD S3210, Rheodyne valve 5210i, and JetStream II column oven). RP18ec Nucleodur columns

(250 × 4.6 mm, 5 μm) from Macherey & Nagel, Düren, Germany were used as analytical HPLC columns along with a RP18 guard column. A ChiralCel OD-H HPLC column (250 × 4.6 mm, 5 μm) was purchased from VWR international, Darmstadt, Germany. Preparative HPLC was performed with a SYKAM HPLC instrument (SYKAM, Fürstenfeldbruck, Germany, gradient pump S1122, DAD S3210, and Rheodyne valve 5330). RP18ec Nucleodur columns (250 × 21 mm, 5 μm as stationary phase) from Macherey & Nagel, Düren, Germany were used as preparative HPLC columns along with Grom Saphir 110C18 (30 × 20 mm, 5 μm) guard columns.

Nor-semimyrtucommulone [(–)-6]: Isobutyryl phloroglucinol (196 mg, 1 mmol) was dissolved in THF (1 mL) under N_2. The solution was cooled to 0 °C, and a freshly prepared solution of (*S*,*S*)-**8**[19a] (0.25 M solution in THF, 13.0 mL, 3 mmol) was added slowly by syringe. The resulting green suspension was stirred at 0 °C for an additional hour. Then, freshly prepared isobutylidene syncarpic acid[10] (0.75 M solution in THF, 2.0 mL, 1.5 mmol) was added dropwise at the same temperature. The stirring was continued for 1 h [monitored by TLC (hexanes/acetone, 1:1, v/v)] and then the reaction mixture was quenched with HCl (1 N aqueous solution that was saturated with NH_4Cl). The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were dried with $MgSO_4$. Filtration and evaporation of the solvent gave the crude product, which was purified by flash chromatography [petroleum ether (b.p. 40–60 °C)/acetone, 3:1 (v/v)] to give nor-semimyrtucommulone [(–)-**6**, 330 mg, 77% yield] as a yellow powder. $[\alpha]_D^{20}$ = –13 (*c* = 4.6, MeOH). The ^{1}H NMR spectrum displayed two sets of data in a ratio of 1:1, which probably stemmed from two rotamers. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 14.35 (br. s, 0.5 H, OH), 13.67 (br. s, 1 H, OH), 5.68 and 5.67 (s, 1 H, 5-H), 4.22 and 4.17 (sept, $^3J_{H2'',H3''\text{-}H4''}$ = 6.8 Hz, 1 H, 2″-H), 3.85 and 3.81 (d, $^3J_{H1',H8'}$ = 10.9 Hz, 1 H, 1′-H), 3.36–3.17 (m, 1 H, 8′-H), 1.31–1.24 and 1.23–1.15 (2 m, 12 H, 11′-H, 12′-H, 13′-H, 14′-H), 1.14 and 1.13 (d, $^3J_{H4'',H2''}$ = 6.8 Hz, 3 H, 4″-H), 1.09 and 1.08 (d, $^3J_{H3'',H2''}$ = 6.8 Hz, 3 H, 3″-H), 0.82 and 0.81 (d, $^3J_{H9',H8'}$ = 6.4 Hz, 3 H, 9′-H), 0.70 and 0.67 (d, $^3J_{H10',H8'}$ = 6.5 Hz, 3 H, 10′-H) ppm. Also, the ^{13}C NMR spectrum showed almost every signal as doubled, which indicated two different rotamers. ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 218.7 (C-5′), 212.1 and 211.8 (C-1″), 195.0 and 192.5 (C-7′), 167.38 and 167.36 (C-3′), 166.64 and 166.58 (C-4), 164.1 (C-6), 163.5 (C-2), 114.2 and 113.7 (C-3), 113.3 and 113.1 (C-2′), 106.8 and 106.2 (C-1), 98.4 and 97.4 (C-5), 53.54, 53.36, 53.34, and 53.26 (C-4′, C-6′), 43.6 and 43.4 (C-1′), 40.3 and 40.2 (C02″), 27.6 and 27.2 (C-8′), 27.4, 27.2, 26.9, 26.8, 26.7, 26.6 (C-11′, C-12′, C-13′, C-14′), 23.8, 23.7, and 23.6 (C-4″, C-3″), 21.5 and 21.2, 20.7 and 20.4 (C-9′, C-10′) ppm. A detailed analysis of the product was carried out after the cyclization to **2**. HRMS: calcd. for $C_{24}H_{33}O_7$ $[M + 1]^+$ 433.2221; found 433.2220.

Cyclization of Nor-semimyrtucommulone [(–)-6] to (+)-2: For analytical purposes, nor-semimyrtucommulone (50.0 mg, 115 μmol) was dissolved in dry benzene (5 mL). *para*-Toluenesulfonic acid (50 mg, 288 μmol) was added, and the mixture was heated at reflux for 1 h. After cooling to room temperature, the mixture was washed with a saturated solution of $NaHCO_3$ and dried with $MgSO_4$. The solvents were evaporated to dryness to yield crude MC B (50.0 mg), which was purified by flash chromatography [petroleum ether (b.p. 40–60 °C)/acetone, 9:1 (v/v)] to give (+)-**2** (43 mg, 91%, 62%*ee*) as a white solid. $[\alpha]_D^{20}$ = +105 (*c* = 3.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.36 (s, 1 H, C-6–OH), 6.59 (br. s, 1 H, C-4–OH), 6.32 (s, 0.16 H, 5-H), 6.30 (s, 0.84 H, 5-H), 4.38 (d, $^3J_{H1',H8'}$ = 3.5 Hz, 0.85 H, 1′-H), 4.35 (d, $^3J_{H1',H8'}$ = 3.8 Hz, 0.18 H, 1′-H), 3.95–3.83 (m, 1 H, 2″-H), 1.92 (d sept, $^3J_{H1',H8'}$ = 3.8 Hz and $^3J_{H8',H9'\text{-}H10'}$ = 6.8 Hz, 1 H, 8′-H), 1.62 (s, 3 H, 12′-H), 1.46 (s, 3 H, 14′-H), 1.43 (s, 0.51 H, 11′-H), 1.42 (s, 2.49 H, 11′-H), 1.39 (s, 3 H, 13′-H), 1.26 (d, $^3J_{H2'',H4''}$ = 6.5 Hz, 3 H, 4″-H), 1.24 (d, $^3J_{H2'',H3''}$ = 7.0 Hz, 3 H, 3″-H), 0.84 (d, $^3J_{H8',H9'}$ = 7.3 Hz, 3 H, 9′-H) 0.79 (d, $^3J_{H8',H10'}$ = 7.0 Hz, 3 H, 10′-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.7 (C-5′), 208.9 (C-1″), 198.8 (C-7′), 168.2 (C-3′), 164.7 (C-4), 159.5 (C-6), 153.4 (C-2), 112.1 (C-2′), 103.8 (C-3), 103.6 (C-1), 100.6 (C-5), 56.1 (C-6′), 47.28 (C-4′), 39.7 (C-2″), 34.8 (C-8′), 31.4 (C-1′), 25.1 (C-12′), 24.97 (C-14′), 24.94 (C-11′), 24.2 (C-13′), 20.85 (C-3″), 18.8 (C-9′), 18.7 (C-10′), 17.7 (C-4″) ppm. HRMS: calcd. for $C_{24}H_{31}O_6$ $[M + 1]^+$ 415.2115; found 415.2112. HPLC (ChiralCel OD-H, *i*PrOH/*n*-hexane, 30:70, 0.5 mL/min, 15 °C): t_R = 7.34 min (minor) and 9.71 min (major).

Myrtucommulone A [(+)-1a and 1b]: Compound (–)-**6** (183 mg, 0.4 mmol) was dissolved in THF (1 mL) under N_2. The solution was cooled to 0 °C, and a freshly prepared solution of (*R*,*R*)-**8**[19a] (0.25 M solution in THF, 5.2 mL, 1.2 mmol) was added slowly through a syringe. The resulting yellow-greenish suspension was stirred for 1 h at 0 °C. Then, freshly prepared isobutylidene syncarpic acid[10] (0.8 M solution in THF, 1.0 mL, 0.8 mmol) was added dropwise at the same temperature. The stirring was continued overnight at 0 °C [monitored by TLC (hexanes/acetone, 3:1, v/v)]. After the starting material was consumed, the reaction was quenched with HCl (1 N solution that had been saturated with NH_4Cl). The resulting solution was extracted with diethyl ether (3 × 50 mL) and dried with $MgSO_4$. Evaporation of the solvent yielded crude myrtucommulone A, which was purified by flash chromatography [petroleum ether (b.p. 40–60 °C)/acetone, 3:1 (v/v)] to give myrtucommulone A [206 mg, 77%, mixture of **1a** (70%*ee*) and *meso* **1b** (59:41)] as a yellow powder. $[\alpha]_D^{20}$ = +22 (*c* = 2.08, MeOH). The ^{1}H and ^{13}C NMR spectra were as complex as the NMR spectra of the racemic material, which was probably because of the presence of rotamers and keto-enol tautomers. A detailed analysis was carried out after the cyclization to **9**. HRMS: calcd. for $C_{38}H_{53}O_{10}$ $[M]^+$ 669.3633; found 669.3628.

Cyclization of Myrtucommulone A (1) to 9: For analytical purposes, the mixture of (+)-**1a** and **1b** (50.0 mg, 75 μmol) was dissolved in dry benzene (20 mL). *para*-Toluenesulfonic acid (65 mg, 342 μmol) was added, and the mixture was heated at reflux for 1 h. After cooling to room temperature, the mixture was washed with a saturated solution of $NaHCO_3$ and dried with $MgSO_4$. The solvents were evaporated to dryness to yield crude PMCA (**9**, 48.0 mg), which was purified by flash chromatography [petroleum ether (b.p. 40–60 °C)/acetone, 9:1 (v/v)] to give a diastereomeric mixture of **9** (41.0 mg, 87%). HRMS: calcd. for $C_{38}H_{49}O_8$ $[M + 1]^+$ 633.3422; found 633.3415. A sample was purified by preparative HPLC (Nucleodur RP18ec, MeOH/H_2O, 90:10) to yield (+)-**9a** (70%*ee*) and **9b**. Data for (+)-**9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (br. s, 1 H, OH), 4.53 (d, $^3J_{H1',H8'}$ = $J_{H1''',H8'''}$ = 3.5 Hz, 0.27 H, 1′-H and 1‴-H), 4.47 (d, $^3J_{H1',H8'}$ = $^3J_{H1''',H8'''}$ = 3.3 Hz, 1.65 H, 1′-H and 1‴-H), 3.24–3.11 (m, 1 H, 2″-H), 2.02–1.89 (m, 2 H, 8′-H and 8‴-H), 1.54 (s, 6 H, 12′-H and 11‴-H), 1.45 (m, 6 H, 13′-H and 14‴-H), 1.44–1.38 (m, 12 H, 11′-H and 12‴-H, 14′-H and 13‴-H), 1.28–1.22 (m, 6 H, 3″-H and 4″-H), 0.88–0.74 (m, 12 H, 10′-H and 10‴-H, 9′-H and 9‴-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8 (C-5′ and C-5‴), 204.30 (C-1″), 198.4 (C-7′ and C-7‴), 168.6 (C-3′ and C-3″), 151.8 (C-4), 147.6 (C-2 and C-6), 110.9 (C-3 and C-5), 110.0 (C-1), 108.5 (C-2′ and C-2‴), 55.9 (C-6′ and C-6‴), 47.5 (C-4′ and C-4‴), 42.7 (C-2″), 35.1 (C-8′ and C-8‴), 32.4 (C-1′ and C-1‴), 25.2 (C-12′ and C-11‴), 24.81 (C-13′ and C-14‴), 24.79 (C-11′ and C-12‴), 24.4 (C-14′ and C-13‴), 19.1 (C-10′ and C-10‴), 18.7 (C-9′ and C-9‴), 18.0 (C-3″

and C-4′′) ppm. HPLC (ChiralCel-OD H, *i*PrOH/*n*-hexane, 30:70, 0.5 mL/min, 15 °C): t_R = 6.56 min (major) and 8.66 min (minor). Data for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (br. s, 1 H, OH), 4.59 (d, $^3J_{H1',H8'} = {}^3J_{H1''',H8'''}$ = 3.8 Hz, 2 H, 1′-H and 1′′′-H), 3.19 (sept, $^3J_{H2'',H3''-H4''}$ = 7.0 Hz 1 H, 2′′-H), 2.06–1.90 (m, 2 H, 8′-H and 8′′′-H), 1.52 (s, 6 H, 12′-H and 12′′′-H), 1.44 (s, 6 H, 13′-H and 13′′′-H), 1.38 (s, 6 H, 11′-H and 11′′′-H), 1.36 (s, 6 H, 14′-H and 14′′′-H), 1.29 (d, $^3J_{H3''-H4'',H2''}$ = 7.0 Hz, 6 H, 3′′-H and 4′′-H), 0.86 (d, $^3J_{H9',H8'} = {}^3J_{H9''',H8'''}$ = 6.8 Hz, 6 H, 9′-H and 9′′′-H), 0.79 (d, $^3J_{H10',H8'} = {}^3J_{H10''',H8'''}$ = 6.8 Hz, 6 H, 10′-H and 10′′′-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8 (C-5′ and C-5′′′), 205.30 (C-1′′), 198.6 (C-7′ and C-7′′′), 169.1 (C-3′ and C-3′′′), 152.4 (C-4), 147.5 (C-2 and C-6), 111.2 (C-3 and C-5), 110.4 (C-1), 108.5 (C-2′ and C-2′′′), 56.0 (C-6′ and C-6′′′), 47.5 (C-4′ and C-4′′′), 43.3 (C-2′′), 35.1 (C-8′ and C-8′′′), 32.4 (C-1′ and C-1′′′), 24.9 (C-12′ and C-12′′′), 24.77 (C-14′ and C-14′′′), 24.75 (C-11′ and C-11′′′), 24.3 (C-13′ and C-13′′′), 19.1 (C-10′ and C-10′′′), 18.8 (C-9′ and C-9′′′), 17.7 (C-3′′ and C-4′′) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra as well as HRMS spectra are provided for all key intermediates and final products.

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