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A short eight-steps total synthesis of racemic asteriscunolide C

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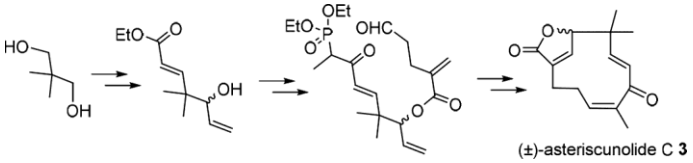
ABSTRACT

A concise total synthesis of racemic asteriscunolide C in eight steps has been described starting from neopentane diol involving an efficient Yamaguchi esterification using an aldehyde-

acid, intramolecular Horner-Wittig-Emmons olefination and a late stage ring-closing metathesis to construct the strained 11-membered ring with one *Z*- and two *E*-double bonds.

GRAPHICAL ABSTRACT



KEYWORDS: asteriscunolides, Horner-Wittig-Emmons, macrolide, racemic synthesis, ring-closing metathesis

Introduction

San Feliciano *et al.*[1] isolated the sesquiterpene lactones asteriscunolides A-D, **1**-**4** (**Figure 1**) from *Asteriscus aquaticus L*. Asteriscunolides possess the humulene **5** skeleton with a strained 11-membered ring. (−)-Asteriscunolide A **1** induces apoptosis[2] (programmed cell death) of human melanoma, leukemia and cells that overexpress antiapoptotic proteins, namely Bcl-2 and Bcl-x(L). All cell lines were sensitive to this compound, with IC_{50} values of approximately 5 μM. The cyctotoxicity levels of asteriscunolides were much higher than those of the common antitumor agent like Cisplatinum for the cancer cell lines, namely human lung carcinoma (A-549), human colon carcinoma (HT-29) and human melanoma (MEL-28).[3] Asteriscunolide D **4** was most potent followed by A **1** and C **3**.

The synthetic attempts on these molecules are rather scarce.[4] The first total synthesis of asteriscunolide D was reported by Trost and co-workers[4a] employing a thionium ion mediated formal aldol reaction followed by thioether activation-elimination sequence to generate the final C-6 *E*-double bond of asteriscunolide D. Subsequently, a chiral pool D-pentolactone based

synthesis involving ring-contracting ring-closing metathesis (RCM) was employed by us in the synthesis of (−)-ateriscunolide C.[4b] Recently, the asteriscunolides and related molecules are synthesized efficiently by Li *et al.* based on a metathesis cascade.[4c]

The inherent ring strain to accommodate one or more *E*-double bonds in the macrocycle imposes a major impediment in the synthesis of these medium ring compounds. Ring-closing metathesis (RCM)[5] is a reaction of choice to generate olefinic bonds in macrocycle synthesis.[6] The outcome of olefin geometry depends largely on ring size and in most cases with medium rings favouring the *Z*-olefin stereochemistry. Thus, it should be possible to generate either of the two *Z*-bonds in asteriscunolide A or the *Z*-bonds in asteriscunolides B and C (**Figure 1**).

Results and Discussion

We designed a non-chiral pool approach to the synthesis of racemic asteriscunolide C starting from neopentanediol **11** which has the gem-dimethyl group that is required in the target molecule as shown in our retrosynthetic analysis in Scheme 1. The alcohol **9** was designed by phosphonate addition to ester **10** which in turn could be easily derived from neopentane diol **11**. The phosphonate **7** was planned through Yamaguchi esterification of alcohol **9** and aldehyde-acid **8**. The bicyclic and highly strained 11-membered ring in **3** was visualized from macrolactone **6** through RCM. The 12-membered macrolactone **6** could be achieved from phosphonate **7** through intramolecular Horner-Wittig-Emmons (HWE)-olefination. The use of ester-aldehyde **8** circumvents any protecting group manipulations unlike in our earlier synthesis[4b] and hence compound **7** could be directly taken for HWE-olefination.

The forward synthesis was initiated from neopentanediol **11**. Diol **11** was oxidized to dialdehyde and subsequent same pot selective HWE-olefination with triethylphosphonoacetate

efficiently delivered compound **12** (72%) in one step. The dialdehyde from **11** was quite stable, perhaps the gem dimethyl group possibly prevented aldol-type reaction. Selective addition of vinyl-Grignard delivered **10**in 88% yield. MOM-ether protection of free hydroxyl group to **13** (90%) and successive two steps: *n*-BuLi mediated addition of $(EtO)_2P(O)CH_2CH_3$[7] followed by MOM-ether deprotection, led to alcohol fragment **9** (**13** to **9**, 81%). For subsequent reaction we considered a aldehyde-acid **8** as the esterification partner (Scheme 2). The latter was prepared from commerically available δ-valerolactone **14**. α-Methylenation[8] of **14** gave **15** (70%) and subsequent hydrolysis and alcohol oxidation provided **8** as an equilibrium mixture of **8a** and **8b** (1.5:1, 68% overall).[9] The Yamaguchi esterification[10] of aldehyde-acid **8** with alcohol **9** provided the ester **7**in 74% yield which on direct intramolecular HWE-olefination[11] under dilution provided the inseparable mixture of **6a**/**6b** (1:1) in 77% yield. Unlike our earlier approach[4b] the use of compound **8** directly for the synthesis of the aldehyde **7** circumvents any protecting group involvement and hence **7** can be used for direct HWE-olefination without involving deprotection-oxidation steps. The final step was similar to our earlier approach[4b] leading to asteriscunolide **3**in overall 8 steps from **11**. The final RCM[12] reaction was attempted on the mixture of **6a**/**6b** using Grubbs IInd generation catalyst which delivered only (±)-asteriscunolide C **3**in 42% yield (84% based on the presence of **6b** in the substrate mixture). Astericunolide D was not obtained, neither could we isolate the precursor **6a** from the RCM reaction. The spectral and analytical data of **3** were in excellent agreement with that reported in literature.[1b]

Conclusion

In summary, a concise total synthesis of racemic asteriscunolide C has been achieved in eight steps. Neopentanediol served as the source for preparation of intermediate **9** with the

gemdimethyl group. The acid-aldehyde partner **8** for esterification was prepared from δ-valerolactone and could give directly the aldehyde **7** for subsequent intramolecular HWE-olefination. The late stage RCM reaction led to the strained 11-membered ring. The synthesis is completed in 8 steps and 11.0% overall yield.

Experimental

Experimental Procedure for the synthesis of

2-Methylene-5-oxopentanoic acid (8a) and 6-hydroxy-3-methylenetetrahydro-2H-pyran-2-one (8b)

To the lactone **15** (0.2g , 1.78 mmol, 1.0 equiv), $LiOH.H_2O$ (1.79g , 42.8 mmol, 24.0 equiv), MeOH (16mL), THF (8mL) and H_2O (4mL) were added and the reaction mixture was then stirred for 24h at room temperature. Then MeOH and THF were evaporated in vacuum and the resulting residue was diluted with cold H_2O (5.0mL) and EtOAc (5.0mL). After acidification with 2N HCl (pH 4-5), the solution was extracted with EtOAc (3 × 10mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to give the acid-alcohol (0.2g , 87%) as gummy solid. ^{1}H NMR ($CDCl_3$, 400MHz): δ 6.19 (s, 1H) 6.59 (s, 1H) 3.65−3.53 (m, 2H) 2.36−2.25 (m, 2H) 1.72−1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 171.3, 139.6, 126.8, 61.4, 30.9, 27.6.

The acid-alcohol (0.2g , 1.54 mmol, 1.0 equiv) was treated with Dess-Martin periodinane (0. 978g , 2.31 mmol, 1.5 equiv) in dry CH_2Cl_2 (15mL) at 0°C. The resulting mixture was stirred at room temperature for 3h . After completion of the reaction (checked by TLC), the mixture was

filtered through celite pad and then concentrated. The residue was passed through a short pad of silica gel and eluted with petroleum ether/EtOAc (1:1) to give the equilibrium mixture **8** (0.154g , 78%) as colorless oil. Data for **8a**: ^{1}H-NMR (400MHz , $CDCl_3$): 9.78 (s, 1H) 6.35 (s, 1H) 5.73 (s, 1H) 2.69−2.59 (m, 4H); ^{13}C -NMR (100MHz , $CDCl_3$): 201.2, 172.2, 139.1, 128.5, 42.5, 29.7; Data for **8b**: ^{1}H-NMR (400MHz , $CDCl_3$): 6.31 (s, 1H) 5.68 (s, 1H) 4.88 (t, *J* = 5.1Hz , 1H) 2.46−2.38 (m, 2H) 1.92−1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 171.5, 138.1, 127.4, 100.7, 32.7, 24.3.

(6E,9E)-7,11,11-Trimethyl-3-methylene-12-vinyloxacyclododeca-6,9-diene-2,8-dione (6a) (1:1) mixture with (6Z,9E)-7,11,11-Trimethyl-3-methylene-12-vinyloxacyclododeca-6,9-diene-2,8-dione (6b)

To a solution of K_2CO_3 (77mg , 0.558 mmol, 6.0 equiv) and 18-crown-6 (0.296g , 1.12 mmol, 12.0 equiv) in toluene (50mL) at 60 °C was added a solution of aldehyde **7** (40mg , 0.093 mmol) in toluene (15mL) over period of 4h . The resulting solution was stirred at 60 °C for 12h . It was then quenched with sat. aq. NH_4Cl (5mL) and the solution extracted with EtOAc (3 × 20mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give a mixture of **6a:6b** (1:1, by ^{1}H-NMR, 20.9mg , 77%) as colorless oil.

Data of mixture: ^{1}H NMR ($CDCl_3$, 400MHz): δ 6.68 (d, *J* = 16.2Hz , 1H) 6.29−6.21 (m, 3H) 6.03−5.99 (m, 3H) 5.96−5.77 (m, 2H) 5.62 (s, 1H), 5.51−5.47 (m, 2H) 5.42 (d, *J* = 6.8Hz , 1H) 5.36−5.29 (m, 4H), 5.03 (d, *J* = 6.8Hz , 1H) 2.91−2.85 (m, 1H), 2.61−2.10 (m, 7H) 1.87 (s, 3H) 1.79 (s, 3H) 1.15 (s, 3H) 1.12 (s, 3H) 1.09 (s, 3H) 1.08 (s, 3H); IR ($CHCl_3$, cm^{-1}): 3018,

2924, 2856, 1722, 1640, 1465, 1371, 1288, 1184, 1146, 1102, 1021, 990, 940, 669; HRMS (ESI): calcd for $C_{17}H_{23}O_3$ [M + H] + 275.1647; found 275.1656.

(±)-Asteriscunolide C (3)[4b]

To a stirred mixture of **6a** and **6b** (15mg , 0.055 mmol, 1.0 equiv) in dry and degassed toluene (10mL) was added Grubb's IInd generation catalyst (4.6mg , 10mol %). The resulting solution was refluxed for 24h and Grubb's IInd generation catalyst (2.3mg , 5mol %) was added and stirred for another 48h . The reaction mixture was concentrated and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to give (±)-**3** (5.65mg , 84% based on the proportion of **6b** in substrate mixture) as white solid. mp 160−161 ^{o}C; (lit.[3] 164 ^{o}C); ^{1}H NMR ($CDCl_3$, 400MHz): δ 6.97 (s, 1H) 6.28 (d, *J* = 16.5Hz , 1H) 5.91 (d, *J* = 16.5Hz , 1H) 5.48 (bd, *J* = 11.6Hz , 1H) 4.71 (s, 1H) 2.54−1.76 (m, 4H) 1.87 (s, 3H) 1.37 (s, 3H) 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 202.6, 173.7, 156.4, 149.7, 138.6, 135.6, 129.5, 128.5, 85.6, 40.7, 33.8, 24.6, 22.8, 21.1, 21.0; IR ($CHCl_3$, cm^{-1}): 3022, 2927, 1762, 1655, 1460, 1451, 1368, 1312, 1182, 1053, 895, 855, 669; HRMS (ESI): calcd for $C_{15}H_{19}O_3$ [M + H] + 247.1334; found 247.1328.

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Supporting Information

Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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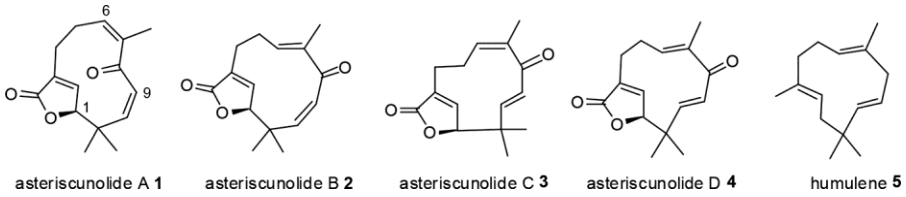
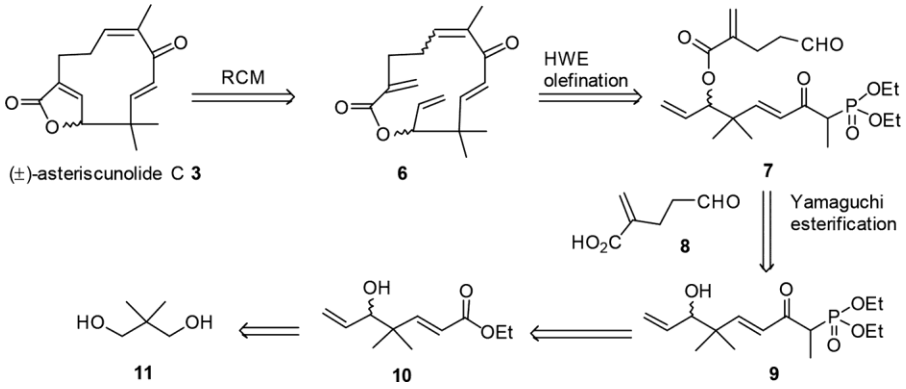
Figure 1. Asteriscunolides A-D **1-4** and related molecule humulene **5**.



Scheme 1. Retrosynthetic route to (±)-asteriscunolide C **3**.



Scheme 2. Synthesis of (±)-asteriscunolide C 3.