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Scalable synthesis of methyl *ent*-isocopalate and its derivatives

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ABSTRACT

An efficient and convenient synthetic route was developed to prepare the tricycle diterpene intermediates **1**–**3** starting from commercially available (−)-sclareol. This improved approach involving four-step reactions provides large-scale (30–40 g) methyl *ent*-isocopalate in 61% overall yield, which could supply sufficient material for the synthesis of marine natural products containing tricyclic diterpenes.

1. Introduction

Spongiane diterpenoids are a class of natural products possessing broad spectrum of biological properties including antifungal, antiinflammatory, antihypertensive, antimicrobial, cytotoxic, antitumor, and anti-HIV activities.[1] Due to their unique stereochemical features, the tricyclic diterpenes intermediates **1**–**3** are frequently used as excellent precursors in the total synthesis of these marine natural products, such as (−)-hyrtiosal,[2–4] luffolide,[1b] and (+)-scalarolide[1h] (Fig. 1).

To the best of our knowledge, three synthetic approaches to methyl *ent*-isocopalate **1** have been presented in the literatures. The first route was described by Minale,[5a] which required five-step reactions starting from the uncommercial grindelic acid. Subsequently, Urones and co-workers published other two approaches. One involved five-step reactions with 45% overall yield from labdanolic acid[5b] and the other embodied eight-step reactions with 49% overall yield using (−)-sclareol as starting material.[5c] However, these procedures mentioned above have some significant drawbacks, such as the use of scarce starting materials (labdanolic acid), long synthetic route (eight steps) and the utilization of hazardous chemicals (diazomethane and organoselenium reagent), which severely limited their applications in the total synthesis of marine natural products. Hence, we developed a practical and convenient synthetic route to prepare methyl *ent*-isocopalate **1** on a large scale. Afterward, isocopalic alcohol **2** and the corresponding aldehyde **3** were readily prepared from methyl *ent*-isocopalate via reduction and oxidation.[5d]

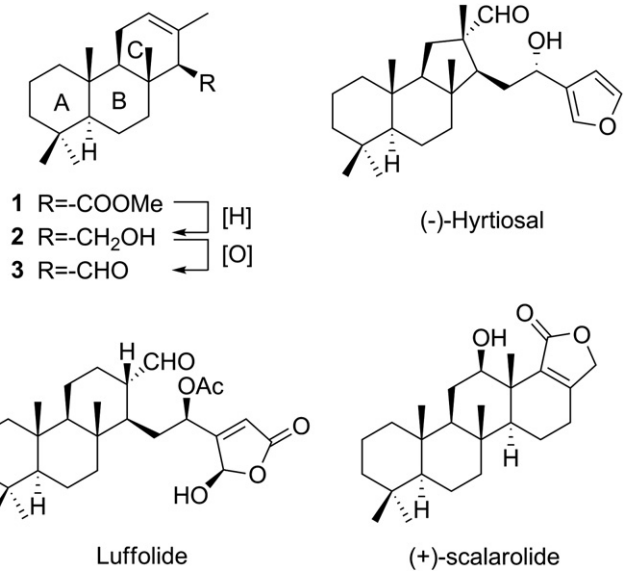

Fig. 1. Tricyclic diterepene intermediates **1**–**3** and the natural products starting from them.

2. Results and discussion

Considering the tricyclic framework and stereochemistry of **1**, our improved route chose commercially available (−)-sclareol as starting material. This novel synthetic strategy involving four-step reactions was shown in Schemes 1 and 2.

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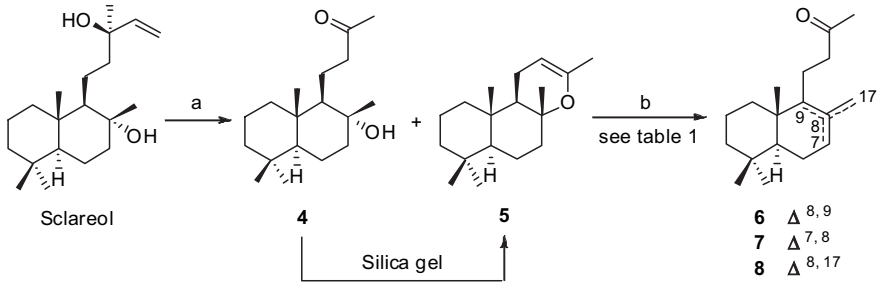
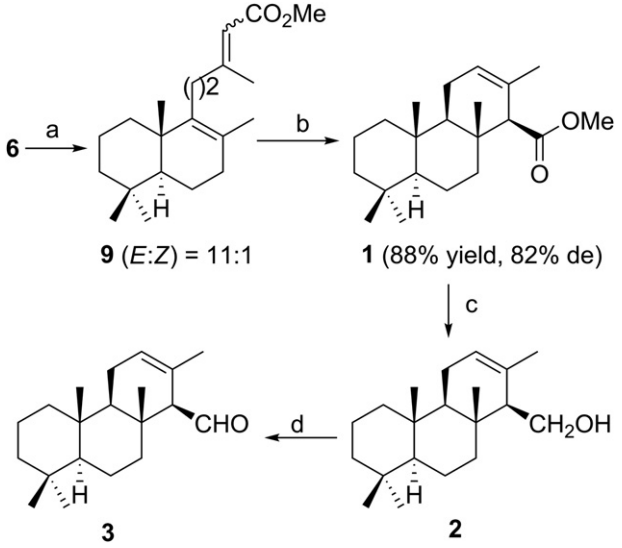


Scheme 1. The synthesis of compound **6**. Reagents and conditions: (a) $KMnO_4$ and $MgSO_4$, acetone, 0 °C to rt, 90%; (b) I_2, PhMe, reflux, 78%.



Scheme 2. Synthesis of methyl *ent*-isocopalate and the corresponding alcohol and aldehyde. Reagents and conditions: (a) NaH, $(EtO)_2P(O)CH_2CO_2Me$, THF, −15 °C, quant.; (b) HCOOH, 80 °C, 88%; (c) and (d) see Ref. 5d.

Our approach commenced with a degradative oxidation of (−)-sclareol to afford methyl ketone **4** according to the established procedure.[6] Furthermore, we found that using finely ground powder of $KMnO_4$ and $MgSO_4$ could greatly improve the yield from 80 to 90%. Compound **4** is unstable, which can easily cyclize and dehydrate to afford sclareol oxide **5** in petroleum ether,[7] benzene[8] or pyridine.[9] And the facile conversion of **4** to **5** also takes place in the presence of mineral acid,[7] on silica gel,[10] or at a higher tempertaure.[8]

The further dehydration of **4** and **5** was liable to provide a mixture of Δ8-labden-13-one **6** and Δ7-labden-13-one **7** in moderate overall yield according to the known procedure.[6a,11] Hoping to achieve a more desirable result, we screened the reaction conditions to optimize the yield and regioselectivity of the product. To our delight, refluxing of **4** and **5** in toluene for 3 h in the presence of catalytic amount of iodine was found to be the most favorable dehydration condition, which afforded **6** as a single product in 78% yield. The optimized conditions and results were outlined in Table 1.

With a reliable preparation to obtain the single compound **6** in hand, we turned our attention to the formation of α,β-unsaturated ester. At this stage, we were disappointed to find that all attempts to afford ester **9** from compound **6** and stable ylide methyl (triphenylphosphoranylidene)-acetate were unsuccessful. However, the replacement of methyl (triphenyl-phosphoranylidene)-acetate with methyl diethylphosphonoacetate via Horner–Emmons reaction could smoothly provide the expected α,β-unsaturated ester **9** in nearly quantitative yield with high regioselectivity (*E*/*Z*=11:1, determined by HPLC), which was superior to the result by using isodrimenol as starting material (*E*/*Z*=7:2).[12] Finally, the unsaturated ester **9** was readily cyclized with formic acid to obtain methyl *ent*-isocopalate **1** in 88% yield, whose physical properties were identical to those previously reported[5a] (details were described in the Supplementary data). The corresponding alcohol **2** and aldehyde **3** were prepared according to the reference from **1**.[5d]

Table 1
Optimization for dehydration of compound **4** and **5**

Entry	Conditions	Temp	Yield[a] (%)
1	$SOCl_2/Py/CH_2Cl_2$	−78 °C	61 (**6**+**7**+**8**)
2	HI/C_6H_6	rt	55 (**6**+**7**)
3	I_2/C_6H_6	Reflux	75 (**6**+**7**)
4	I_2/PhMe	Reflux	78 (**6**)

[a] Isolated yield through flash chromatograph, and the ratio of 6:7 was determined by ^1H NMR.

3. Conclusion

In summary, a practical and concise approach has been developed to synthesize methyl *ent*-isocopalate **1**, isocopalic alcohol **2**, and the corresponding aldehyde **3** from (−)-sclareol in short steps. Each step proceeds to give high yields, which are adequate for large-scale (30–40 g) preparation.

4. Experimental section

4.1. General information

Commercial reagents and solvents were used without further purification unless otherwise mentioned. All anhydrous solvents were prepared according to the reported procedures and distilled under argon prior to use. All the stable compounds were characterized by IR, MS, ^1H, and ^{13}C NMR. Melting points were determined on a digital melting point apparatus WRS-113 and are uncorrected. ^1H and ^{13}C NMR spectra were determined on Bruker 400 instruments in $CDCl_3$ using tetramethylsilane as internal reference. Mass spectra were recorded on a Micromass GCT CA055. Infrared spectra were collected on Thermo FT-IR 200 Spectrometer. Optical rotations were measured using Rudolph Research Analytical Automatic Polarimeter III at ambient temperature and 589 nm. HPLC analyses were performed on Agilent Technologies 1200 Series equipped with a Diamonsil C18 column, using a mixture of acetonitrile/water as a mobile phase, at 25 °C. Chiral HPLC analyses were performed on Agilent Technologies 1100 Series equipped with a chiral OD-H column, using a mixture of *n*-hexane/isopropyl alcohol (IPA) as a mobile phase, at 25 °C. The analytical data for the known compounds were found to match with the literature data.

*4.1.1. (+)-8α-Hydroxy-14,15-bisnorlabda-13-one (**4**).* To an ice cooled solution of (−)-sclareol (30.8 g, 0.1 mol) in acetone (400 mL), the finely ground powder of $KMnO_4$ (55.3 g, 0.35 mol) and $MgSO_4$ (60.2 g, 0.5 mol) was added in portions for 2 h. The reaction mixture

was stirred at ambient temperature overnight. The slurry mixture was filtered through a pad of Celite, and the filter cake was washed with acetone (3×200 mL). The combined organic phase was concentrated under reduced pressure below 20 °C, to afford (+)-8α-hydroxy-14,15-bisnorlabda-13-one (**4**), (25.1 g, 90%) as a white solid, which was directly used for the next step reaction without further purification. The pure sample for data collection was recrystallized from hexane. Mp 77.8–78.9 °C (lit.[13] mp 78–80 °C); $[\alpha]_D^{12}$ +5.1 (*c* 1.03, CH_2Cl_2), lit.[8] +6.7; IR (neat) ν_{max} 3498, 1698, 1114 cm^{-1}; MS (EI, *m*/*z*): 280 [M^+].

*4.1.2. (+)-14,15-Bisnorlabda-8-ene-13-one (**6**).* The pink solution of hydroxyl ketone **4** (22.4 g, 0.08 mol) and I_2 (1.0 g, 4.0 mmol) in anhydrous toluene (500 mL) was refluxed with a Dean–Stark trap for 3 h. The solution was diluted with ethyl acetate (200 mL) and washed with 5% $Na_2S_2O_3$ (3×50 mL), H_2O (3×30 mL), and brine (3×30 mL), the organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuum to provide the crude product that was purified through flash chromatography in petroleum ether to afford (+)-14,15-bisnorlabda-8-ene-13-one (**6**), (16.4 g, 78%) as a light yellow oil. $[\alpha]_D^{13}$ +74.5 (*c* 1.05, $CHCl_3$), lit.[14] +78; IR (neat) ν_{max} 2937, 1716, 1461, 1360, 1159, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.94 (s, 3H), 0.96–1.05 (m, 1H), 1.09 (d, *J*=11.6 Hz, 1H), 1.12–1.17 (m, 1H), 1.37–1.40 (m, 1H), 1.42–1.45 (m, 1H), 1.47–1.48 (m, 1H), 1.53 (s, 3H), 1.58–1.61 (m, 1H), 1.63–1.66 (m, 1H), 1.78 (br d, *J*=12.4 Hz, 1H), 1.91–2.02 (m, 2H), 2.14 (s, 3H), 2.16–2.19 (m, 1H), 2.25–2.33 (m, 1H), 2.49 (t, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 19.0, 19.4, 19.9, 21.6, 21.7, 29.8, 33.3, 33.6, 36.9, 39.1, 41.7, 44.6, 52.0, 126.6, 139.2, 209.1; MS (EI, *m*/*z*): 262 [M^+].

*4.1.3. Labda-8,13-diene-15-oic acid, methyl ester (**9**).* To a mixture of sodium hydride (9.3 g, 0.24 mmol, 60% in mineral oil) in anhydrous THF (100 mL) at −25 °C, methyl diethylphosphonoacetate (38 mL, 0.20 mol) was added under nitrogen atmosphere. The reaction was continued to stir at 0 °C for another 30 min. Then a solution of **6** (17.9 g, 0.07 mol) in anhydrous THF (40 mL) was added dropwise over 2 h, the reaction was stirred at ambient temperature overnight, then quenched with saturated NH_4Cl solution, and extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduce pressure to afford α,β-unsaturated ester **9** (21.6 g, 99.6%, *E*/*Z*=11:1 determined by HPLC) as a yellow liquid. $[\alpha]_D^{20}$ +58.7 (*c* 3.09, $CHCl_3$), lit.[5a] +50.8; IR (neat) ν_{max} 2945, 1725, 1650, 1387, 1148, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.90 (s, 3H), 0.96 (s, 3H), 1.11–1.20 (m, 3H), 1.27–1.31 (m, 1H), 1.39–1.44 (m, 2H), 1.47–1.53 (m, 2H), 1.59 (s, 3H), 1.64–1.70 (m, 2H), 1.82 (br d, *J*=12.0 Hz, 1H), 1.93–2.17 (m, 4H), 2.20 (s, 3H), 3.70 (s, 3H), 5.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.0, 19.5, 20.1, 21.7, 26.4, 33.3, 33.6, 39.1, 41.6, 41.8, 50.8, 51.9, 114.5, 126.7, 139.5, 161.1, 167.4; MS (EI, *m*/*z*): 318 [M^+].

*4.1.4. Methyl ent-isocopalate (**1**).* A solution of 2.7 g (8.6 mmol) of compound **9** in anhydrous formic acid (30 mL) was heated at 80 °C for 3 h. After removal of formic acid under reduced pressure, the yielding solid was recrystallized from MeOH or petroleum ether to give methyl *ent*-isocopalate (**1**), (2.4 g, 88%) as a white solid. Mp 102.2–105.1 °C (lit.[5a] mp 103–105 °C); $[\alpha]_D^{10}$ −59.4 (*c* 2.61, $CHCl_3$), lit.[5a] −50.4; IR (neat) ν_{max} 3438, 2936, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.87 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 1.10–1.18 (m, 2H), 1.25–1.45 (m, 5H), 1.54–1.58 (m, 3H), 1.61 (s, 3H), 1.65–1.74 (m, 2H), 1.96 (br s, 2H), 2.93 (s, 1H), 3.68 (s, 3H), 5.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 15.8, 18.5, 18.6, 21.2, 21.7, 22.7, 33.2, 33.4, 36.5, 37.4, 39.8, 41.8, 51.0, 54.3, 56.4, 62.6, 124.1, 129.0, 173.4; MS (EI, *m*/*z*): 318 [M^+]. The de value of the product was determined by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*-PrOH=30:1, 230 nm, 1 mL/min, 25 °C), 82% de.

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Supplementary data

Copies of ^1H NMR, ^{13}C NMR and HPLC spectra associated with this article can be found in the supplementary content. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.008. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; de Roman, M.; Sanz, F.; Urones, J. G. *Tetrahedron* **2007**, *63*, 8939; (b) Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; De Roman, M.; Urones, J. G. *J. Org. Chem.* **2005**, *70*, 9480; (c) Basabe, P.; Gomez, A.; Marcos, I. S.; Martin, D. D.; Broughton, H. B.; Urones, J. G. *Tetrahedron Lett.* **1999**, *40*, 6857; (d) Gonzalez-Sierra, M.; Kaufman, T.; Ruveda, E. A. *J. Chem. Soc., Chem. Commun.* **1986**, 418; (e) Mischne, M. P.; Sierra, M. G.; Ruveda, E. A. *J. Org. Chem.* **1984**, *49*, 2035; (f) Gonzalez, M. A. *Tetrahedron* **2008**, *64*, 445; (g) Sierra, G.; Mischne, M. P.; Ruveda, E. A. *Synth. Commun.* **1985**, *15*, 727; (h) Meng, X. J.; Liu, Y.; Fan, W. Y.; Hu, B.; Du, W. T.; Deng, W. P. *Tetrahedron Lett.* **2009**, *50*, 4983.
2. (a) Lunardi, I.; Santiago, G. M. P.; Imamura, P. M. *Tetrahedron Lett.* **2002**, *43*, 3609; (b) Basabe, P.; Diego, A.; Diez, D.; Marcos, I. S.; Mollinedo, F.; Urones, J. G. *Synthesis* **2002**, 1523; (c) Basabe, P.; Diego, A.; Diez, D.; Marcos, I. S.; Urones, J. G. *Synlett* **2000**, 1807.
3. Du, L.; Shen, L. L.; Yu, Z. G.; Chen, J.; Guo, Y. W.; Tang, Y.; Shen, X.; Jiang, H. L. *ChemMedChem* **2008**, *3*, 173.
4. Sun, T.; Wang, Q.; Yu, Z. G.; Zhang, Y.; Guo, Y. W.; Chen, K. X.; Shen, X.; Jiang, H. L. *ChemBioChem* **2007**, *8*, 187.
5. (a) Cimino, G.; De Rosa, D.; De Stefano, S.; Minale, L. *Tetrahedron* **1974**, *30*, 645; (b) Urones, J. G.; Sexmero, M. J.; Lithgow, A. M.; Basabe, P.; Gomez, A.; Marcos, I. S.; Estrella, A.; Diez, D.; Carballares, S.; Broughton, H. B. *Nat. Prod. Lett.* **1995**, *6*, 285; (c) Urones, J. G.; Marcos, I. S.; Basabe, P.; Gomez, A.; Estrella, A.; Lithgow, A. M. *Nat. Prod. Lett.* **1994**, *5*, 217; (d) Gonzalez Sierra, M.; Cravero, R. M.; Laborde, L. A.; Ruveda, E. A. *J. Chem. Soc., Chem. Commun.* **1984**, 417.
6. (a) Marcos, I. S.; Beneitez, A.; Castaneda, L.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Synlett* **2007**, 1589; (b) Marcos, I. S.; Basabe, P.; Laderas, M.; Díez, D.; Jorge, A.; Rodilla, J. M.; Moro, R. F.; Lithgow, A. M.; Barata, I. G.; Urones, J. G. *Tetrahedron* **2003**, *59*, 2333; (c) Leite, M. A. F.; Sarragiotto, M. H.; Imamuna, P.; Marsaidi, A. J. *J. Org. Chem.* **1986**, *51*, 5409.
7. Bigley, D. B.; Rogers, N. A. J.; Barltrop, J. A. *J. Chem. Soc.* **1960**, 4613.
8. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron* **1993**, *49*, 10405.
9. Bendall, J. G.; Cambie, R. C.; Moratti, S. C.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1995**, *48*, 1747.
10. Marcos, I. S.; Laderas, M.; Diez, D.; Basabe, P.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 5419.
11. Gray, C. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Tetrahedron* **2003**, *59*, 165.
12. Arima, Y.; Kinoshita, M.; Akita, H. *Tetrahedron: Asymmetry* **2007**, *18*, 1701.
13. Barltrop, J. A.; Littlehailes, J. D.; Rushton, J. D.; Rogers, N. A. J. *Tetrahedron Lett.* **1962**, *10*, 429.
14. Mangoni, L.; Belardini, M. *Gazz. Chim. Ital.* **1963**, *93*, 465.