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Expedient route to CDE ring system of schintrilactones through tandem ROM–RCM of a norbornene derivative

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ABSTRACT

A concise synthesis of a highly functionalized tricyclic ring system representing the CDE core of nortriterpenoid schintrilactones A and B is described using a tandem ROM–RCM of a norbornene derivative.

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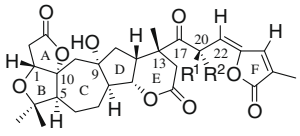
Schintrilactones A **1** and B **2** (Fig. 1) are two nortriterpenoids isolated from *Schisandra chinensis*, a Chinese medicinal plant of *Schisandracea* family.[1] Structures of these compounds were established based on spectroscopic data and density functional theory calculations of circular dichroism. Compounds **1** and **2** possess a highly oxygenated structurally complex carbon skeleton not previously encountered in nature. Interestingly they occur as a slowly interconverting diastereomeric pair at C_{20} stereogenic center. Both these compounds exhibit weak anti-HIV-1 activity.

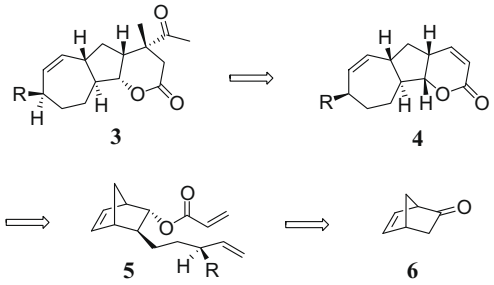
Several compounds[2] isolated from *Schisandracea* family have recently elicited considerable synthetic interest[3] due to their structural complexity and wide ranging biological activity. However, studies toward the synthesis of schintrilactones remained elusive. We herein report preliminary results of our investigation toward the synthesis of schintrilactones culminating in a facile route to the construction of a highly functionalized CDE tricyclic ring system.

Our retrosynthetic analysis (Scheme 1) began with disconnection of C_1–C_{10} and C_{20}–C_{22} bonds of **1** and **2** to lead to the tricycle **3**. While the double bond in the seven-membered ring of **3** can be employed to introduce the C_9 angular OH group through allylic hydroxylation,[4] it can also be used to construct the C_1–C_{10} bond after adjustment of the oxidation level at C_{10}. The substituent 'R' should be a functionalized carbon chain that could be elaborated to construct the B ring. Compound **3** would be obtained from the tricycle **4** through conjugate addition of appropriate nucleophile. The tricycle **4** could in principle be available from tandem ring-opening metathesis (ROM) of the norbornene derivative **5** and bidirectional ring-closing metathesis (RCM) of the resulting tetraene derivative. The norbornene derivative **5** could be expected to be available from 2-norbornenone **6**.



1, $R^1 = CH_3$, $R^2 = H$
2, $R^1 = H$, $R^2 = CH_3$

Figure 1. Structures of schintrilactones.



Scheme 1. Retrosynthetic strategy.

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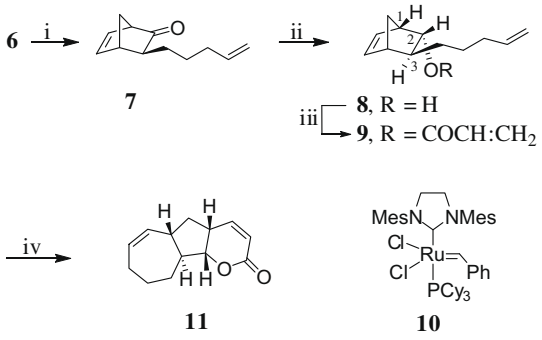


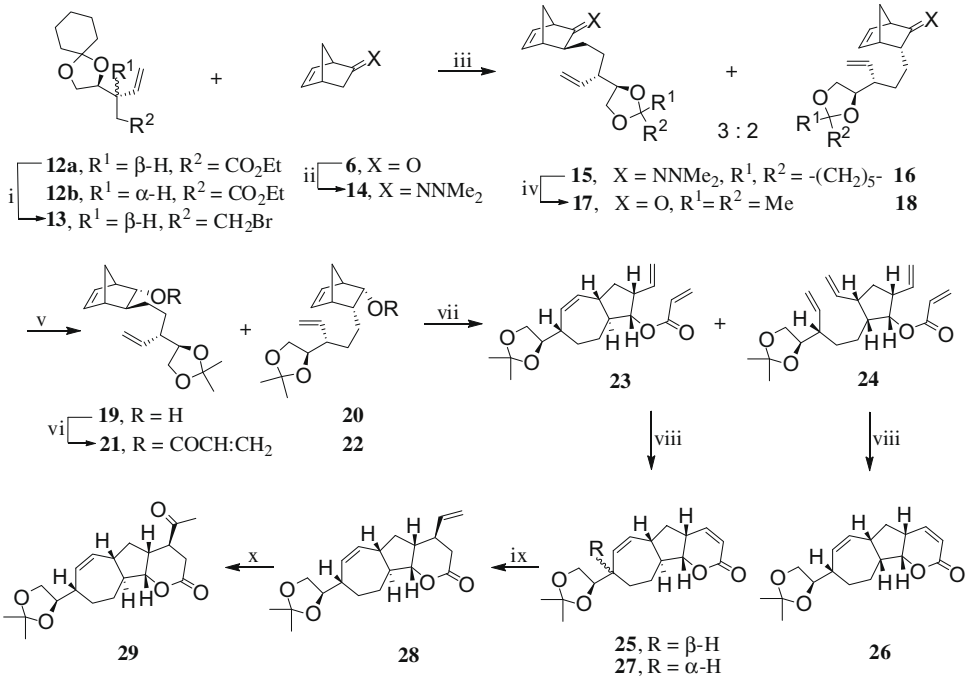
Scheme 2. Synthesis of tricyclic lactone **11**. Reagents and conditions: (i) LDA, 5-bromo-1-pentene, −78 °C, THF/HMPA (3:1), 50%; (ii) $LiAlH_4$, Et_2O, −20 °C, 1 h, 90%; (iii) Et_3N, acryloyl chloride, DCM, 0 °C, 1 h, 95%; (iv) **10** (4 mol %), ethylene, DCM, rt, 8 h, 94%.

In order to demonstrate the feasibility of the above-mentioned synthetic plan toward the construction of CDE ring system of **1** and **2**, we initially focused on metathesis of the norbornene derivative **9**. ROM–RCM of norbornene derivatives with alkyl chains having terminal alkene units has been exploited by us[5] and others[6] for direct construction of a variety of ring systems. In all these cases only simple norbornene derivatives lacking any oxygen functionality in the norbornene core have been employed. Although metathesis of norbornenes with different oxygen functionalities at 2- and 7-position[7] has been investigated, ROM–RCM of norbornene derivatives with oxygen functionality at norbornene core has not been reported.

The compound **9** was prepared as indicated in Scheme 2. Reaction of lithium enolate derived from 2-norbornenone **6** with 5-bromo-1-pentene furnished exclusively the alkylated compound **7** in very good yield. The *exo*-stereochemical assignment to the alkyl group was based on analogy to the formation of *exo*-alkylated products on alkylation of 2-norbornenone with alkyl halides.[8] The carbonyl group was then reduced with $LiAlH_4$ to form the hydroxy compound **8**. The structure of the hydroxy compound was established from comparison of the coupling constant of the C_2–H which appeared at δ 3.8 as a triplet ($J_{1,2} = J_{2,3} = 3.3$ Hz) with that reported in the literature.[9] Treatment of **8** with acryloyl chloride produced the acrylate derivative **9** in 95% yield. Metathesis of **9** was accomplished by treatment of its solution in dichloromethane at rt with Grubbs' catalyst **10** to afford exclusively the tricycle **11**[10] in 94% yield.

The facile ROM–RCM of the norbornene derivative **9** to form the tricycle **11** led us to extend this protocol for the synthesis of a functionalized tricyclic analogue that could be elaborated to the natural products. Toward this end, alkylation of **6** with the enantiopure alkyl bromide **13** was undertaken (Scheme 3). The bromide **13** was prepared from the readily available[11] unsaturated ester **12a** through reduction of the ester functionality followed by treatment of the resulting alcohol with CBr_4–PPh_3. Attempted alkylation of the enolate of 2-norbornenone **6** with bromide **13** led to an intractable mixture from which no alkylation product could be isolated. However, alkylation of the hydrazone **14**[12] with the bromide **13** afforded an inseparable mixture of the alkylated products **15** and **16** in ca. 3:2 ratio in 80% yield. Regeneration of the carbonyl group from the mixture of the hydrazones **15** and **16** on treatment with aqueous acetic acid was accompanied by deketalization to lead to a mixture of the diols. The diol unit in these compounds was protected with 2,2-dimethoxy propane to give a mixture of the norbornenones **17** and **18** in overall good yield. The norbornenones **17** and **18** were then transformed to the metathetic precursors **21** and **22** through reduction ($NaBH_4$) of the carbonyl group followed by reaction of the hydroxy groups in the resulting products with acryloyl chloride.

With the metathetic precursor in hand, we pursued its metathesis. When a mixture of the norbornene derivatives **21** and **22** was treated with Grubbs' catalyst **10** under the condition used for



Scheme 3. Synthesis of enantiopure functionalized CDE ring of schintrilactones. Reagents and conditions: (i) (a) $LiAlH_4$, Et_2O, 0 °C, 1 h, 95%; (b) CBr_4, PPh_3, DCM, 0 °C, 2 h, 90%; (ii) H_2NNMe_2, Δ, quant; (iii) LDA, **13**, 0 °C, 4 h, 80%; (iv) (a) 80% AcOH, rt, 16 h; (b) 2,2-dimethoxy propane, *p*-TSA, DCM, rt, 3 h (70% for two steps); (v) $NaBH_4$, MeOH, −20 °C, 1 h, 80%; (vi) Et_3N, acryloyl chloride, DCM, 0 °C, 1 h, 90%; (vii) Grubbs' I (4 mol %), ethylene, DCM, rt, 12 h, 55% for **23** and 33% for **24**; (viii) **10** (2.5 mol %), DCM, rt, 3 h, 90% for **25** and 80% for **26**; (ix) CH_2:CHMgBr, CuI, TMEDA, −78 °C, 2 h, 75%; (x) $PdCl_2$, CuCl, DMF/H_2O (4:1), O_2, rt, 6 h, 92%.

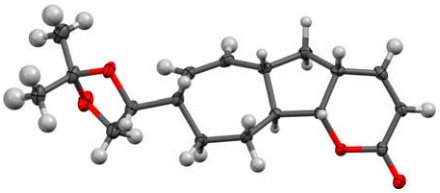


Figure 2. X-ray structure of **25**.

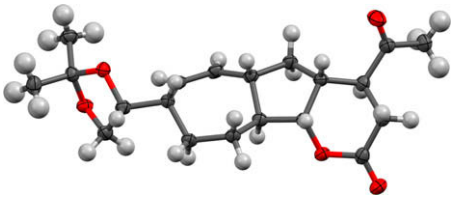


Figure 3. X-ray structure of **29**.

metathesis of **9**, a mixture of tricyclic lactones **25** and **26** was obtained in 80% yield. Although metathesis of **21** and **22** gave directly the tricycles **25** and **26**, separation of **25** from **26** was difficult. However, metathesis of the mixture of **21** and **22** with Grubbs' 1st generation catalyst [$Cl_2Ru(PCy_3)_2$=CHPh] afforded a mixture from which the bicycle **23** and the tetraene **24** could be isolated in 55% and 33% yields, respectively, after column chromatography. Compounds **23** and **24** were then separately allowed to react with Grubbs' catalyst **10** to furnish the pure tricyclic lactones **25** and **26** in 90% and 80% yields, respectively. The structure of the compound **25** was established through its single crystal X-ray analysis (Fig. 2).[13] Thus the minor lactone obtained after metathesis of the mixture of **21** and **22** was assigned the structure **26**. This automatically dictated the structures of the other compounds depicted in Scheme 3. The major tricyclic lactone **25** possesses the desired stereochemistry at three of the four asymmetric centers at the ring fusions. Repeating the reaction sequence presented in Scheme 3 with the bromide prepared from the unsaturated ester **12b**,[11a] the tricyclic lactone analogue **27** with the required C-5 configuration might be obtained.

In order to demonstrate that the lactone **25** can be used for the introduction of the carbon chain toward the total synthesis of **1** and **2**, 1,4-addition of vinylmagnesium bromide to **25** in the presence of CuI was carried out. The lactone **28** was obtained in 75% yield as a single diastereomer. The stereochemical assignment to the lactone **28** is based on its transformation to the keto-lactone **29** using Wacker oxidation.[14] The structure of the compound **29** was established by single crystal X-ray structure (Fig. 3).[13]

In conclusion, we have developed a short route for the synthesis of an enantiomerically pure highly functionalized tricyclic ring system that represents the CDE core of schintrilactones A and B.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.074.

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10. All new compounds were characterized on the basis of IR, ^1H, ^{13}C NMR, and HRMS data. *Spectral data for selected compounds*: *Compound* **8**: IR (liquid film) ν_{max} 3425, 1638, 1356 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.45–6.42 (dd, J = 3.3, 5.5 Hz, 1H), 6.08–6.05 (dd, J = 2.6, 5.5 Hz, 1H), 5.86–5.72 (m, 1H), 5.01–4.90 (m, 2H), 3.88 (t, J = 3.3 Hz, 1H), 2.86 (br s, 1H), 2.47 (br s, 1H), 2.09–2.03 (q, J = 13.0, 2H), 1.65 (br s, 1H), 1.57–1.30 (m, 5H), 0.96–0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9 (CH), 138.8 (CH), 131.8 (CH), 114.5 (CH_2), 79.8 (CH), 50.7 (CH), 48.3 (CH), 47.3 (CH), 45.2 (CH_2), 34.1 (CH_2), 33.9 (CH_2), 27.9 (CH_2); FAB MS, *m/z*: 201 (M^++Na), 161 (M^+–H_2O+H). *Compound* **11**: IR (liquid film) ν_{max} 2922, 1714, 1390, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.71–6.66 (dd, J = 4.0, 10.0 Hz, 1H), 5.88 (br d, J = 10.0 Hz, 1H), 5.84–5.76 (m, 1H), 5.61 (br d, J = 10.6 Hz, 1H), 4.45 (t, J = 8.2 Hz, 1H), 2.82–2.75 (m, 1H), 2.43–2.30 (m, 2H), 2.25–2.15 (m, 1H), 2.08–2.01 (m, 1H), 1.87–1.74 (m, 2H), 1.56–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (CO), 147.9 (CH), 133.6 (CH), 132.9 (CH), 118.4 (CH_2), 86.7 (CH), 51.5 (CH), 41.7 (CH), 37.9 (CH_2), 34.9 (CH), 34.4 (CH_2), 28.5 (CH_2), 25.6 (CH_2); HRMS (ESI) calcd for $C_{13}H_{16}O_2Na$ (M+Na)$^+$, 227.1048; found, 227.1046. *Compound* **25**: mp 121–123 °C, $[\alpha]_D^{25}$ −62.6 (*c* 2.6, $CHCl_3$); IR (KBr) ν_{max} 2930, 1726, 1641, 1373 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.68–6.64 (dd, J = 4.0, 9.9 Hz, 1H), 5.86 (d, J = 10.2 Hz, 1H), 5.68 (br d, J = 12 Hz, 1H), 5.50 (br d, J = 12 Hz, 1H), 4.41 (t, J = 8.2 Hz, 1H), 4.04–3.96 (m, 2H), 3.59–3.52 (m, 1H), 2.80–2.75 (m, 1H), 2.48–2.37 (m, 2H), 2.35–2.27 (m, 2H), 1.88–1.84 (m, 1H), 1.74–1.65 (m, 2H), 1.56–1.43 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.10–0.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (CO), 147.7 (CH), 134.4 (CH), 132.5 (CH), 118.1 (CH), 108.8 (C), 86.1 (CH), 78.9 (CH), 67.7 (CH_2), 50.8 (CH), 46–3.5 (CH), 41.4 (CH), 37.5 (CH_2), 34.5 (CH), 33.8 (CH_2), 28.2 (CH_2), 26.5 (CH_3), 25.1 (CH_3); HRMS (ESI) calcd for $C_{18}H_{24}O_4Na$ (M+Na)$^+$, 327.1572; found, 327.1572. *Compound* **26**: mp 82–84 °C, $[\alpha]_D^{25}$ 149.4 (*c* 1.4, $CHCl_3$); IR (KBr) ν_{max} 2923, 1729, 1650, 1368 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.68–6.63 (dd, J = 4.2, 9.9 Hz, 1H), 5.85–5.81 (dd, J = 2.1, 9.9 Hz, 1H), 5.59 (br d, J = 11.4 Hz, 1H), 5.51–5.45 (ddd, J = 2.4, 3.6, 13.2 Hz, 1H), 4.51–4.46 (dd, J = 6.9, 8.4 Hz, 1H), 4.05–3.98 (m, 1H), 3.94–3.89 (dd, J = 6.2, 8.1 Hz, 1H), 3.56–3.51 (dd, J = 7.0, 7.8 Hz, 1H), 2.74–2.68 (m, 1H), 2.40–2.25 (m, 3H), 2.20–2.05 (m, 2H), 1.73–1.64 (m, 2H), 1.60–1.38 (m, 1H), 1.33 (s, 3H), 1.27 (s, 3H), 1.20–1.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (CO), 147.5 (CH), 133.7 (CH), 130.9 (CH), 118.3 (CH), 108.8 (C), 86.6 (CH), 77.4 (CH), 67.5 (CH_2), 51.1 (CH), 41.1 (CH), 40.9 (CH), 38.1 (CH_2), 34.9 (CH), 28.8 (CH_2), 27.0 (CH_2), 26.6 (CH_3), 25.4 (CH_3); HRMS (ESI) calcd for

$C_{18}H_{24}O_4Na$ $(M+Na)^+$, 327.1572; found, 327.1575. *Compound* **29**: mp 95–98 °C; $[\alpha]_D^{25}$ −118.9 (*c* 3.2, $CHCl_3$); IR (KBr) ν_{max} 2918, 1741, 1718, 1371 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (br d, *J* = 12.0 Hz, 1H), 5.52 (br d, *J* = 12.0 Hz, 1H), 4.24–4.21 (t, *J* = 8.4 Hz, 1H), 4.02–3.98 (m, 2H), 3.61–3.54 (t, *J* = 10.2 Hz, 1H), 2.74–2.66 (m, 1H), 2.62–2.56 (dd, *J* = 2.5, 15.9 Hz, 1H), 2.47–2.44 (m, 2H), 2.41–2.29 (m, 2H), 2.29–2.17 (m, 2H), 2.22 (s, 3H), 1.89–1.85 (m, 1H), 1.67–1.55 (m, 2H), 1.51–1.43 (m, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 1.13–1.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9 (CO), 171.7 (CO), 134.4 (CH), 132.7 (CH), 108.9 (C), 86.9 (CH), 78.7 (CH), 67.3 (CH_2), 51.1 (CH), 49.3 (CH), 43.5 (CH), 42.9 (CH), 38.1 (CH_2), 37.8 (CH), 34.4 (CH_2), 31.9 (CH_2), 29.4 (CH), 28.4 (CH_2), 26.6 (CH_3), 25.2 (CH_3); HRMS (ESI) calcd for $C_{20}H_{28}O_5Na$ $(M+Na)^+$, 371.1834; found, 371.1833.

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13. X-ray single crystal data were collected using Mo Kα (λ = 0.71073 Å) radiation on a BRUKER APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, and structure solution/refinement were carried out using the software package of SMART APEX. The structure was solved by direct method and refined in a routine manner. Non-hydrogen atoms were treated anisotropically. All hydrogen atoms were geometrically fixed. CCDC (CCDC Nos. 724514 for **25** and 768857 for **29**) contains the Supplementary data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). *Crystal data for compound* **25**: a block-shaped colorless crystal (0.24 × 0.12 × 0.08) was analyzed. $C_{18}H_{24}O_4$, FM = 304.37, orthorhombic, space group P2(1)2(1)2(1), *a* = 6.0303(7), *b* = 7.7941(9), *c* = 33.720(4) Å, *V* = 1584.9(3) $Å^3$, *T* = 100 K, *Z* = 4, D_c = 1.276 g cm^{-3}, *F* (0 0 0) = 656, λ (Mo Kα) = 0.71073 Å, μ Mo Kα/mm^{-1} = 0.089, 3476 reflections measured, 3131 observed (I > 2σ (I)) 295 parameters; R_{int} = 0.0386, R_1 = 0.0355; wR_2 = 0.0865 (I > 2r (I)), with GOF = 1.057. *Crystal data for compound* **29**: a block-shaped colorless crystal (0.20 × 0.08 × 0.06) was analyzed. $C_{20}H_{28}O_5$, FM = 348.42, monoclinic, space group C2, *a* = 19.154(3), *b* = 6.7026(10), *c* = 14.327(2) Å, *V* = 1806.1(5) $Å^3$, *T* = 120 K, *Z* = 4, D_c = 1.281 g cm^{-3}, *F* (0 0 0) = 752, λ (Mo Kα) = 0.71073 Å, μ Mo Kα/mm^{-1} = 0.091, 2835 reflections measured, 2394 observed (I > 2σ (I)) 223 parameters; R_{int} = 0.0806, R_1 = 0.0377; wR_2 = 0.0861 (I > 2r (I)), with GOF = 0.996.
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