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A novel asymmetric approach to a densely functionalized lactarane ring system through a domino ring opening–ring closing metathesis of a norbornene derivative

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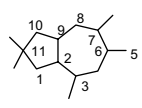
ABSTRACT

A novel route for the synthesis of a highly functionalized lactarane skeleton in enantiomerically pure form is described via ROM–RCM of an appropriately constructed norbornene derivative as the key step.

Lactaranes are a class of sesquiterpenes possessing the carbocyclic skeleton **1** as the core structure. They are isolated from the *Lactarius* and *Russulaceae* species of mushroom. Recently, a number of highly functionalized lactaranes such as 1,2-dehydrolactarolide A **2**, lactarorufin A **3**, and 3-*O*-ethyl lactarolide B **4** have been isolated[1] from a mushroom of the *Russulaceae* family. Lactaranes continue to be synthetic targets due to their wide ranging biological activities such as antifeedant, antimicrobial, and mutagenic.[2] A number of approaches[3] for the syntheses of some structurally simple lactaranes have been reported. These approaches lack generality and are not suitable for the synthesis of the more functionalized lactaranes.



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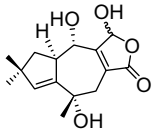

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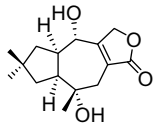

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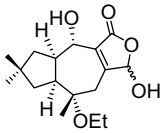

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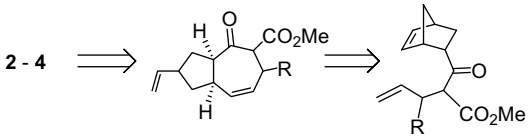
Herein we report a general stereocontrolled approach for the construction of a highly functionalized lactarane skeleton in enantiomerically pure form via a domino ring opening metathesis–ring closing metathesis (ROM–RCM)[4] of suitably constructed norbornene derivatives.

In the retrosynthetic pathway (Scheme 1), bicycle **5** was identified as the hydroazulenoid portion of the lactaranes. In principle, the butenolide ring could be annulated onto **5** by employing the carbomethoxy group and the R substituent. A masked carbonyl group as R would allow construction of the butenolide unit. The bicycle **5** would be available through ROM–RCM of the appropriately functionalized norbornene derivative **6**.

ROM–RCM of norbornene derivatives having alkene chains at C-2 has been shown to proceed efficiently to produce fused bicycles,[4a–g] bridged ring systems,[4h] and spirocyclic systems.[4i] The efficiency of olefin metathesis is influenced[5] to a great extent



5 **6**

Scheme 1. A general retrosynthetic analysis for lactaranes.

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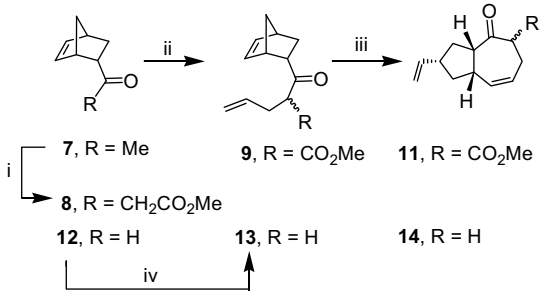
by a number of parameters including the nature of the functional groups present in the substrate. Although metathesis of substrates having a variety of functional groups has been investigated, there is no report on metathesis of alkenes possessing an enolizable β-keto-ester. Since the projected synthesis involves metathesis of alkenes having this unit, initially a structurally simple analogue **9** was chosen in order to determine the efficiency of the metathesis reaction. Compound **9** was prepared as a 1:1 diastereoisomeric mixture in excellent yield by allylation of the sodium enolate of **8** which in turn was obtained from the norbornene derivative **7** (Scheme 2). Metathesis of compound **9** on treatment with Grubbs' catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ **10** at rt was found to be complete in 1 h and produced the bicycle **11** in near quantitative yield. In contrast, metathesis of the decarbomethoxy analogue **13** prepared from the aldehyde **12**, as described in Scheme 2, required more than 15 h for completion to produce **14** in 60% yield. It appears from this investigation that an enolizable β-keto-ester unit in the alkene chain might facilitate metathesis of norbornene derivatives.

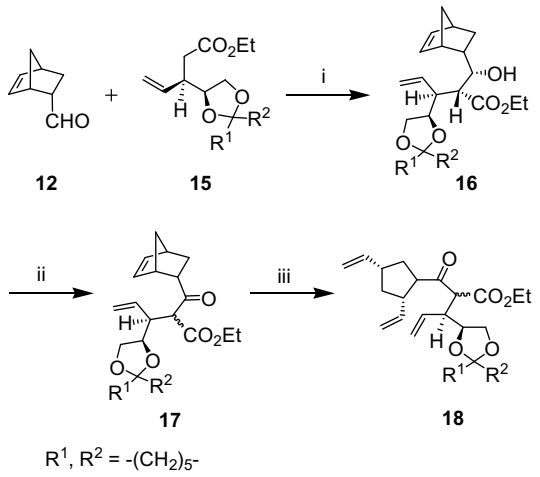
After establishing that an enolizable β-keto-ester might have significant influence on ROM–RCM of norbornene derivatives, we next embarked upon the synthesis of the lactarane skeleton. The required β-keto-ester **17** was prepared as follows (Scheme 3): An aldol-type condensation of the aldehyde **12** with the lithium enolate of the optically pure ester **15**[6] produced mainly diastereoisomer **16** along with a minor amount of the other possible diastereoisomer as an inseparable mixture (ca. 85:15) in 78% isolated yield. The assignment of stereochemistry to **16** is based on the stereochemical oucome observed[7] for an analogous aldol condensation of the enolate of the same ester **15** with aromatic aldehydes. Oxidation of the hydroxy compound **16** with Dess–Martin periodinane (DMP) afforded **17** in 90% yield as a 1:1 diastereoisomeric mixture probably arising through epimerisation during oxidation.

Metathesis of the norbornene derivative **17** with Grubbs' catalyst **10** at rt was complete in 1 h, and the product obtained in near quantitative yield was characterized as the ring-opened product **18** as a 1:1 diastereoisomeric mixture. Attempted ring closure of **18** on prolonged treatment with catalyst **10** at rt or even at elevated temperature was unsuccessful.

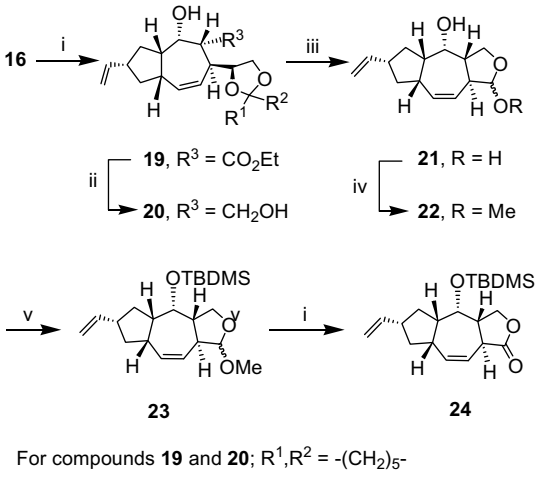
The hydroxy compound **16** was next subjected to metathesis with Grubbs' catalyst **10** under the above conditions. Gratifyingly, the hydroazulene derivative **19**[8] was obtained in 65% yield as a crystalline solid, mp 93–95 °C (Scheme 4). Both the 5- and 7-membered rings in **19** are correctly functionalized for the synthesis of lactaranes. For annulation of the butenolide unit, the hydroxy-ester **19** was first reduced with $LiAlH_4$ to afford the diol **20** in 90% yield as a white solid, mp 133–134 °C. Acid induced deketalisation followed by periodate cleavage of the resulting vicinal diol unit gave the lactol **21** (60% in two steps). Treatment of the lactol **21** with



Scheme 2. Reagents and conditions: (i) NaH, THF, Me_2CO_3, 70 °C, 4 h 60%; (ii) NaH, THF, 0 °C to rt, $CH_2{:}CHCH_2Br$, 3 h, 80%; (iii) 5 mol % cat **10**, C_2H_4, CH_2Cl_2, rt; (iv) (a) $CH_2{:}CHCH_2CH_2Br$, Mg, THF, 0 °C to rt, 3 h, 72%; (b) CrO_3, 7.0 N H_2SO_4, 0 °C, 30 min, 80%.



Scheme 3. Reagents and conditions: (i) LDA, THF, HMPA, −78 °C, 15 min, 78%; (ii) Dess–Martin periodinane, CH_2Cl_2, 30 min, 90%; (iii) 10 mol % cat **10**, C_2H_4, CH_2Cl_2, rt, 1 h, quant.



Scheme 4. Reagents and conditions: (i) 7 mol % cat **10**, C_2H_4, CH_2Cl_2, rt, 8 h, 65%; (ii) LAH, Et_2O, 1 h, 95%; (iii) (a) AcOH–H_2O (3:1), 8 h; (b) $NaIO_4$, THF-H_2O (3:1), 60% two steps; (iv) MeOH, HCl (cat), 70%; (v) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 85%; (vi) (a) 70% aq AcOH; (b) PDC, CH_2Cl_2, 75% two steps.

MeOH–HCl provided the acetal **22** in 70% yield as an epimeric mixture. The hydroxyl group in **22** was then protected as the silyl ether **23**. Deacetalization of **23** with 70% aqueous acetic acid at rt followed by oxidation with PDC afforded the tricyclic lactone **24** in 75% yield. The IR absorption at 1776 cm^{-1} indicated that the lactone unit was *trans*-fused. Further, analysis of the HSQC, H–H COSY and NOESY (Fig. 1a) spectra confirmed the structure of the tricyclic

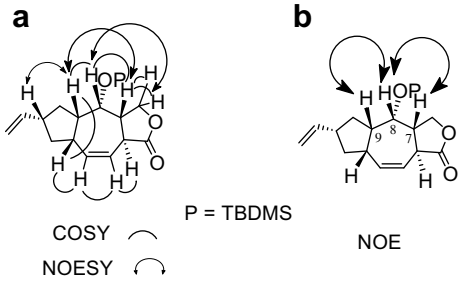


Figure 1.

compound as **24**. Significant NOE correlations (Fig. 1b) between the H7–H8 (1.61%) and H8–H9 (1.68%) corroborated the above structural assignment. The hydroxy lactone **24** is appropriately functionalized and can be considered as an advanced intermediate for elaboration to lactaranes.

In conclusion, we have developed a short and efficient protocol for the enantiopure construction of the densely functionalized tricyclic skeleton present in lactaranes. The key steps involve a diastereoselective aldol-type condensation of an optically pure ester enolate with norbornene-2-carbaldehyde and ROM–RCM of the resulting norbornene derivative.

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.2008.07.083.

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8. All new compounds were characterized by IR, ^{1}H, ^{13}C NMR and HRMS spectroscopy. Physical data for selected compounds: Compound **16**: $[\alpha]_D^{24}$ +7.1 (*c* 3.35, $CHCl_3$); IR (neat): 1732, 3444 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, t, *J* = 6.8 Hz), 1.35 (4H, br s), 1.50 (3H, br s), 1.54 (6H, br s), 1.78–1.90 (1H, m), 2.22–2.32 (1H, m), 2.65–2.76 (4H, m), 3.00 (1H, m), 3.59–3.62 (1H, m), 3.90–3.94 (1H, m), 4.09–4.18 (2H, m), 4.22–4.33 (1H, m), 5.06–5.22 (2H, m), 5.88–6.00 (2H, m), 6.13–6.23 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 23.7 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 29.5 (CH_2), 34.6 (CH_2), 35.7 (CH_2), 42.3 (CH), 42.4 (CH), 44.3 (CH), 44.7 (CH), 49.8 (CH_2), 51.1 (CH), 60.7 (OCH_2), 66.7 (OCH_2), 75.3 (OCH), 75.5 (OCH), 109.4 (C), 118.5 (CH_2), 131.6 (CH), 136.3 (CH), 138.2 (CH), 174.9 (CO); HRMS (ESI) calcd for $C_{23}H_{34}O_5Na$ $(M+Na)^+$, 413.2304; found 413.2308. *Compound* **18** (1:1 diastereomeric mixture): IR (neat) 1709, 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14–1.24 (3H, m), 1.32 (2H, br s), 1.48 (4H, br s), 1.53 (5H, br s), 1.67–2.04 (3H, m), 2.42–2.51 (1H, m), 2.76–2.97 (2H, m), 3.21–3.32 (1H, m), 3.57 (1H, t, *J* = 7.6 Hz), 3.70 (1H, d, *J* = 8.8 Hz), 3.90 (2H, m), 4.08–4.17 (2H, m), 4.83–5.14 (6H, m), 5.48–5.81 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 14.2 (CH_3), 23.8 (CH_2), 24.0 (CH_2), 25.2 (CH_2), 34.4 (CH_2), 34.5 (CH_2), 34.6 (CH_2), 35.7 (CH_2), 35.8 (CH_2), 39.7 (CH_2), 43.6 (CH), 45.2 (CH), 47.6 (CH), 53.2 (CH), 57.3 (CH), 61.4 (OCH_2), 62.4 (OCH), 62.5 (OCH), 66.4 (OCH_2), 74.8 (OCH), 109.5 (C), 109.6 (C), 113.6 (CH_2), 115.5 (CH_2), 119.9 (CH_2), 132.8 (CH), 133.9 (CH), 134.0 (CH), 139.0 (CH), 139.1 (CH), 141.6 (CH), 141.7 (CH), 168.0 (CO), 168.5 (CO), 205.1 (CO), 205.4 (CO); HRMS (ESI) calcd for $C_{25}H_{36}O_5Na$ $(M+Na)^+$, 439. 2460; found 439.2462. *Compound* **19**: mp 93–95 °C; $[\alpha]_D^{25}$ +75.1 (*c* 0.93, $CHCl_3$); IR (KBr) 1732, 3431 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (3H, t, *J* = 7.0 Hz), 1.34 (2H, br s), 1.53 (5H, br s), 1.60 (5H, br s), 1.99–2.06 (1H, m), 2.10 (1H, br s), 2.18–2.22 (1H, m), 2.37–2.44 (2H, m), 2.98 (2H, br s), 3.53 (1H, t,*J* = 7.7 Hz), 3.60 (1H, t, *J* = 5.0 Hz), 3.93 (1H, t, *J* = 7.2 Hz), 4.07 (1H, t, *J* = 6.2 Hz), 4.19 (2H, q, *J* = 7.0 Hz), 4.87–5.02 (2H, m), 5.50 (2H, br s) 5.74–5.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (CH_3), 23.8 (CH_2), 24.0 (CH_2), 25.2 (CH_2), 34.4 (CH_2), 35.9 (CH_2), 38.3 (CH), 39.0 (CH_2), 40.0 (CH), 41.0 (CH_2), 41.5 (CH), 43.6 (CH), 48.0 (CH), 60.8 (OCH_2), 66.7 (OCH_2), 74.0 (OCH), 75.6 (OCH), 109.6 (C), 113.3 (CH_2), 124.9 (CH), 136.7 (CH), 141.9 (CH), 174.1 (CO); HRMS (ESI) calcd for $C_{23}H_{34}O_5Na$ $(M+Na)^+$, 413.2304; found 413.2305. *Compound* **22**: IR (neat) 3436 cm^{-1}; ^{1}H NMR: δ 1.48–1.54 (1H, m), 1.67 (1H, br s), 1.70–1.77 (1H, m), 2.11–2.20 (2H, m), 2.62–2.66 (2H, m), 2.98 (1H, br s), 3.05–3.09 (1H, m), 3.38 (3H, s), 3.83 (1H, t, *J* = 8.5 Hz), 4.00 (1H, q, *J* = 8.4 Hz), 4.11 (1H, br s), 4.81–4.98 (3H, m), 5.34 (1H, td, *J* = 2.3, 11.3 Hz), 5.70 (1H, td, *J* = 3.0, 11.2 Hz), 5.73 (1H, m); ^{13}C NMR: δ (for the major epimer) 34.4 (CH_2), 39.2 (CH), 40.5 (CH), 41.4 (CH_2), 41.6 (CH), 41.9 (CH), 50.1 (CH), 55.0 (OCH_3), 69.0 (OCH_2), 69.5 (OCH), 106.3 (CH), 112.4 (CH_2), 127.0 (CH), 136.3 (CH), 144.3 (CH); HRMS (ESI) calcd for $C_{15}H_{22}O_3Na$ $(M+Na)^+$, 273.1467; found 273.1462. *Compound* **24**: $[\alpha]_D^{25}$ +16.7 (*c* 0.46, $CHCl_3$); IR (neat) 1776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.36–1.44 (1H, m), 1.52–1.75 (2H, m), 2.09–2.16 (2H, m), 2.64–2.79 (2H, m), 3.00 (1H, br s), 3.69 (1H, ddd, *J* = 12.4, 6.1, 3.0 Hz), 4.02 (1H, dd, *J* = 8.2, 2.9 Hz), 4.07 (1H, t, *J* = 3.4 Hz), 4.17 (1H, t, *J* = 8.0 Hz), 4.82–4.95 (2H, m), 5.41 (1H, td, *J* = 11.2, 2.4 Hz), 5.75–5.81 (1H, m), 5.88 (1H, td, *J* = 11.2, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.7 (CH_3), −3.9 (CH_3), 18.3 (C), 26.1 (CH_3), 33.8 (CH_2), 38.4 (CH), 39.6 (CH), 40.2 (CH), 41.3 (CH_2), 43.3 (CH_2), 50.5 (CH), 67.5 (OCH_2), 68.8 (OCH), 112.6 (CH_2), 125.4 (CH), 137.9 (CH), 144.2 (CH), 178.1 (CO); HRMS (ESI) calcd for $C_{20}H_{32}O_3SiNa$ $(M+Na)^+$, 321.2018; found 321.2015.