DOI: 10.1002/ejoc.200600760

Total Synthesis of (+)-Migrastatin

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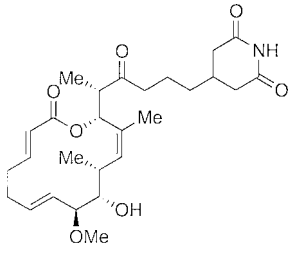
Keywords: Ring-closing metathesis / Crotyltitanation / Crotylstannylation / Cross-metathesis / Total synthesis

(+)-Migrastatin, an antimetastatic agent, was synthesized by using three ruthenium-catalyzed metathesis reactions: a ring-closing metathesis (RCM) to control the (*Z*)-trisubstituted double bond at C11–C12, another RCM at C6–C7 to establish the macrolactone core, and a cross-metathesis to install the glutarimide side chain at C16–C17. The stereogenic centers at C9, C10, C13, and C14 were introduced by using two stereoselective crotylmetalations.

Introduction

(+)-Migrastatin is a naturally occurring macrolide, isolated from broth cultures of two strains of *Streptomyces*.[1,2] This compound has been shown to inhibit cell migration in a wide range of tumor cell lines, at micromolar concentrations. Because of the unusual mode of action of migrastatin and its potential use in anticancer treatment, we decided to devise a convergent and flexible synthesis, giving access to both the natural product itself as well as to a number of analogues. To the best of our knowledge, only one synthesis of migrastatin has been reported in the literature to date, and the synthesis of analogues has also been achieved.[3,4]

The structure of migrastatin was established unambiguously by X-ray analysis of a derivative.[1d] This compound consists of a 14-membered lactone linked to an alkylglutarimide side chain. The molecule contains five stereogenic centers, two (*E*)-disubstituted double bonds, and one (*Z*)-trisubstituted double bond (Figure 1).



(+)-Migrastatin (**1**)

Figure 1. Structure of migrastatin (**1**).

Results and Discussion

The key steps in our synthesis of migrastatin were based on the use of three ruthenium-catalyzed metathesis reactions: one ring-closing metathesis (RCM) to control the (*Z*)-double bond at C11–C12, another RCM to establish the macrolactone core and to control the (*E*)-double bond at C6–C7, and a cross-metathesis (CM) to install the glutarimide side chain by forming the C16–C17 bond. The stereogenic centers at C9, C10 and C13, C14 were controlled by using two enantio- and diastereoselective crotylmetalations of aldehydes.

As depicted in Scheme 1, the macrocyclic lactone could be the result of a chemoselective RCM applied to diene **A**. This diene could in turn be formed by the esterification of 2,6-heptadienoic acid (**18**) with alcohol **B**. The construction of fragment **B** relies on the chemoselective CM reaction between allylglutarimide (**17**) and vinyl ketone **C** (C7–C16) followed by a chemoselective hydrogenation of the double bond of the enone.

The C7–C16 fragment (fragment **C**) contains all the five stereogenic centers of migrastatin as well as the (*Z*)-trisubstituted C11–C12 double bond. Enone **C** could be obtained from olefin **D** by functional transformation of the C15–C16 double bond. The *anti* relationship at C13–C14 in fragment **D** should be obtained by using an *anti*-selective enantio- and diastereoselective crotylmetalation applied to an aldehyde of type **E**. This aldehyde, which possesses the (*Z*)-configuration at C11–C12 and is required for the structure of migrastatin, could be obtained by reduction of the unsaturated lactone **F**. This lactone could be built by a RCM involving diene **G**, which possesses the methacrylate moiety that is a precursor of the (*Z*)-C11–C12 double bond. A diene of type **G** should be easily prepared from the corresponding *syn*,*syn*-stereotriad **H**, which could be obtained by using a stereoselective crotylmetalation applied to aldehyde **J**. Finally, aldehyde **J** could be synthesized from the commercially available methyl (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**2**) (Scheme 2).

Our synthesis of migrastatin started from methyl ester **2**, which was transformed to alcohol **3** in four steps (58% yield). After oxidation of alcohol **3** under Swern conditions,

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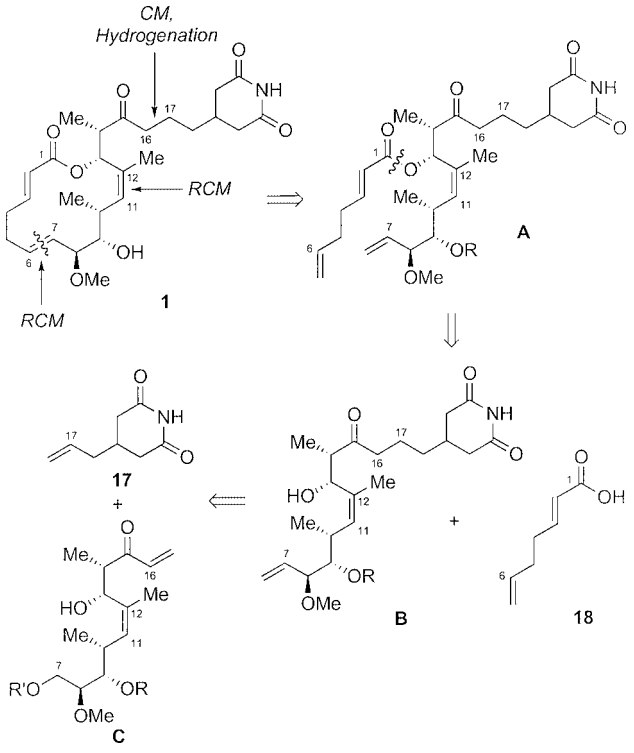
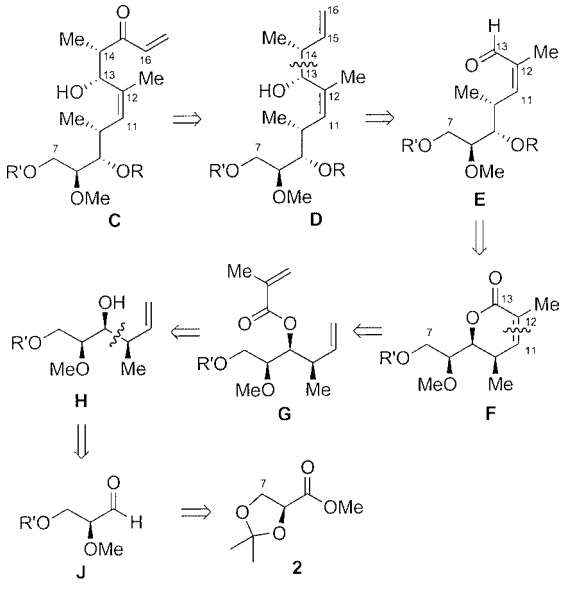


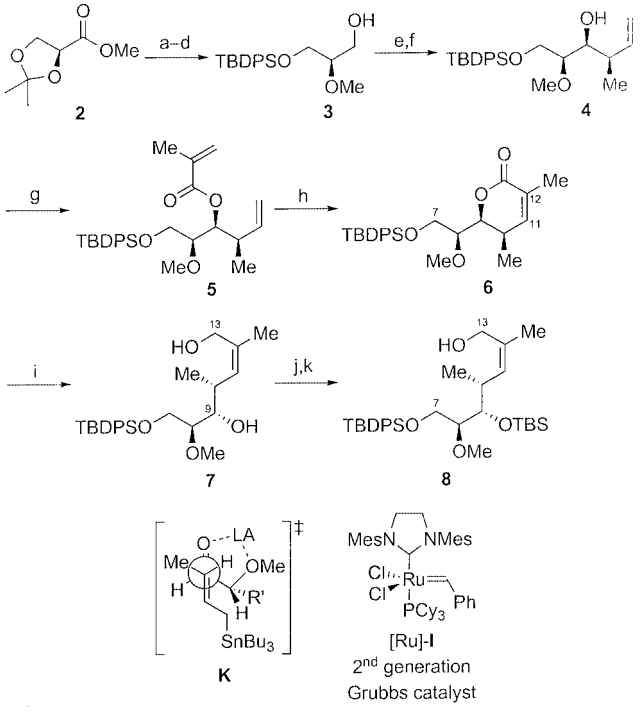
Scheme 1. Retrosynthetic plan for the synthesis of migrastatin (**1**). CM = Cross-Metathesis; RCM = Ring-Closing Metathesis.



Scheme 2. Retrosynthetic analysis of fragment **C** (C7–C16).

the resultant crude aldehyde was directly treated with but-2-enyl[tri(*n*-butyl)]stannane (1.5 equiv., CH_2Cl_2, –60 °C) in the presence of $MgBr_2{\cdot}OEt_2$ (2.2 equiv.) to give the *syn*,*syn*-stereotriad **4** in 83% yield with good stereocontrol (*dr* = 90:10).[5,6] The stereochemical outcome of this addition is likely to be the result of an open chair transition state of type **K**, in which both the carbonyl and the methoxy groups of the aldehyde are chelated with $MgBr_2{\cdot}OEt_2$.[5] After esterification of **4** with methacryloyl chloride (Et_3N, DMAP cat, CH_2Cl_2, 0 °C to room temp. 80%), diene **5** was treated with the second-generation Grubbs catalyst [Ru]-**I** (16.5 mol-%) in refluxing CH_2Cl_2 to afford the unsaturated lactone **6** in 65% yield.[7,8] At this point of the synthesis, three of the five stereogenic centers and the trisubstituted (*Z*)-C11–C12 double bond were established.

In order to introduce the remaining two stereogenic centers at C13 and C14, lactone **6** was converted to the (*Z*)-homoallylic alcohol **8** in three steps. After the reduction of lactone **6** with $LiBH_4$ (7 equiv.) in the presence of $CeCl_3{\cdot}7H_2O$ (1 equiv.) in THF/H_2O (4:1) at room temp., diol **7** was isolated in 74% yield.[9] To differentiate the hydroxy groups at C9 and C13, both of them were silylated (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to room temp., 75% yield), and the primary alcohol at C13 was selectively deprotected (THF/H_2O/AcOH, 1:1:3, room temp., 36 h) to produce the allylic alcohol **8** in 75% yield (Scheme 3).

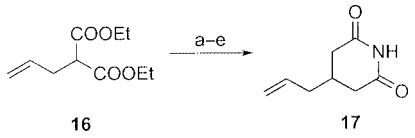


Scheme 3. Synthesis of alcohol **8**. Reagents and conditions: a) *p*TsOH, MeOH/H_2O (1:1), room temp., 83%; b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to room temp. 81%; c) Ag_2O, MeI, MS 4 Å, Et_2O, 40 °C, 96%; d) DIBAL-H, CH_2Cl_2, –78 °C to room temp. 90%; e) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N –78 °C to room temp.; f) $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, –20 °C, then but-2-enyl-[(tri(*n*-butyl)]stannane, –60 °C, 87% (over two steps); g) methacryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temp. 80%; h) [Ru]-**I** (16.5 mol-%), CH_2Cl_2 ($c = 10^{-2}$ M), 40 °C, 144 h, 65%; i) $LiBH_4$ (7 equiv.), $CeCl_3.7H_2O$ (1 equiv.), THF/H_2O (4:1), room temp., 74%; j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to room temp. 75%; k) THF/H_2O/AcOH (1:1:3), 36 h, room temp., 75%. *p*TsOH = *para*-toluenesulfonic acid; TBDPSCl = *tert*-butyldiphenylsilyl chloride; MS = molecular sieves; DIBAL-H = di-isobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Scheme 5 delineates the synthesis of compound **15** (C7–C21 fragment). To control the stereogenic centers at C13 and C14, the allylic alcohol **8** was oxidized to aldehyde **9**

(MnO_2, CH_2Cl_2, room temperature) and then treated directly with the highly face-selective crotyltitanium complex Ti-(*S*,*S*)-**I**,[10] which gave the homoallylic alcohol **10** in 80% yield (from **8**) with good diastereoselectivity (*dr* = 90:10).[11,12] The following step involved the selective oxidative cleavage of the terminal C15–C16 double bond. The hydroxy group at C13 in compound **10** was converted to the corresponding TES ether **11** (TESCl, imidazole, CH_2Cl_2, room temp., 90%) in order to sterically protect the internal double bond at C11–C12 from oxidative cleavage. Therefore, the C15–C16 double bond was chemoselectively transformed to an aldehyde by using a dihydroxylation-oxidative cleavage sequence (OsO_4, *N*-methylmorpholine *N*-oxide, then $NaIO_4$) to produce aldehyde **12** in 80% yield. This aldehyde was then converted to the α,β-unsaturated ketone **13** in two steps by treatment with vinylmagnesium chloride (THF, –78 °C) followed by oxidation of the resultant allylic alcohol (Dess–Martin periodinane, CH_2Cl_2, 0 °C to room temp., 73% yield for the last two steps).[13]

With vinyl ketone **13** (C7–C16 fragment) in hand, enone **15** (C7–C21 fragment) was assembled by using a CM reaction between vinyl ketone **13** and allylglutarimide (**17**), which was prepared in five steps from the commercially available diethyl allylmalonate (**16**) with an overall yield of 20% (Scheme 4).

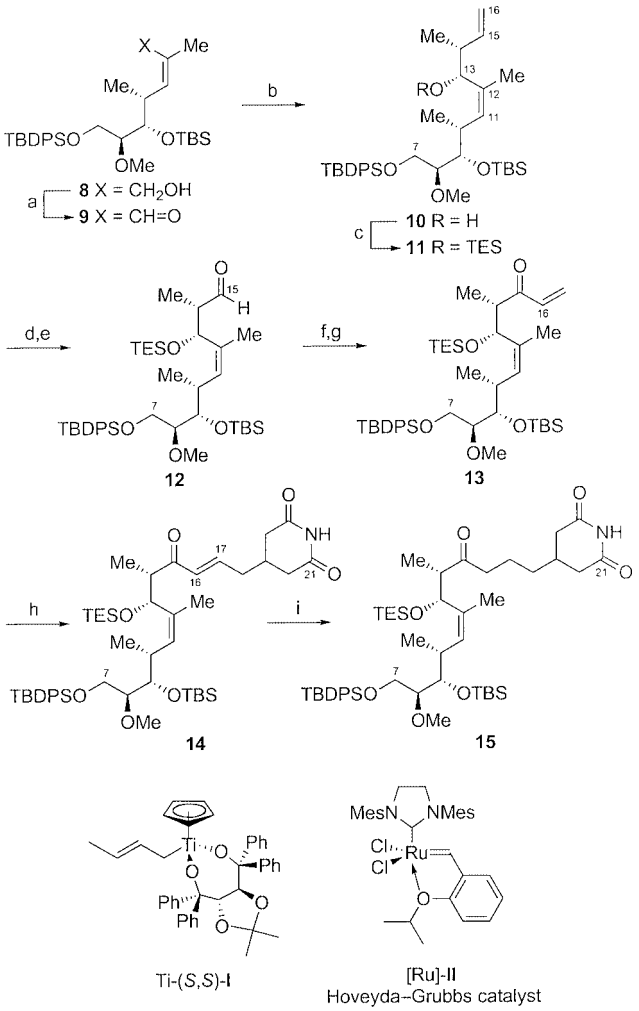


16 17

Scheme 4. Synthesis of allylglutarimide (**17**). Reagents and conditions: a) $LiAlH_4$, Et_2O, 0 °C to room temp. 12 h, 69%; b) *p*TsCl, KOH, THF, 0 °C, 2 h, then room temp., 4 h, 93%; c) NaCN, DMSO, 45 °C, 22 h; d) NaOH, MeOH, reflux, 4 h, 42% yield for the two steps; e) urea, 145 °C, 2 h, then 180 °C, 20 min; 73%. *p*TsCl = *para*-toluenesulfonyl chloride.

When the CM reaction between vinyl ketone **13** and allylglutarimide (**17**) was performed in the presence of Hoveyda–Grubbs catalyst [Ru]-**II**, the CM product **14** was isolated with a moderate yield (32%) ([Ru]-**II**, 30 mol-%; **17**, 3 equiv; CH_2Cl_2, room temp., 72 h).[14–16] In order to complete the synthesis of **15** (C7–C21 fragment), enone **14** was selectively hydrogenated (Pd/C 5%, H_2, AcOEt, room temp., 10 h) to afford **15** in 96% yield (Scheme 5).

Having synthesized the C7–C21 fragment (compound **15**), we could consider the construction of the macrolactone core leading to the complete synthesis of migrastatin. After selective deprotection of the hydroxy group at C13 in compound **15** (THF/H_2O/AcOH, 1:1:3, room temp., 80% yield), the obtained alcohol was transformed to ester **20** in 74% yield by using the freshly prepared mixed anhydride **19** (toluene, room temp., 48 h).[17] In order to prepare the RCM precursor **21**, ester **20** was selectively deprotected at C7 by employing ammonium fluoride in methanol. The resulting primary alcohol was oxidized to the corresponding aldehyde, which was directly treated under Takai conditions to afford diene **21** in 44% yield (over three steps).[18–20] As described previously,[3] diene **21** was treated with [Ru]-**I**

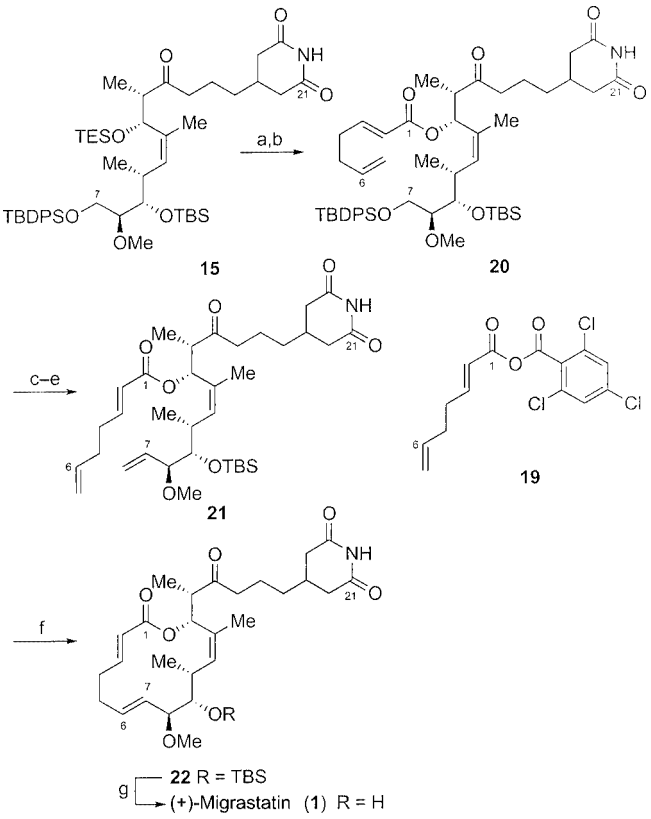


Scheme 5. Synthesis of fragment C7–C21 (**15**). Reagents and conditions: a) MnO_2, CH_2Cl_2, room temp., 16 h; b) Ti-(*S*,*S*)-**I**, (1.4 equiv.), Et_2O, –78 °C, 24 h, 80% over two steps; c) TESCl, CH_2Cl_2, room temp., 16 h, 90%; d) OsO_4 (4 mol-%), NMO (1 equiv.), *t*BuOH/H_2O (1:1), room temp., 24 h; e) $NaIO_4$ (4.5 equiv.), THF/H_2O (1:1), room temp., 10 h, 80% over two steps; f) vinylmagnesium chloride (3 equiv.), –78 °C, THF, 0.5 h; g) Dess–Martin periodinane (2 equiv.), CH_2Cl_2, 0 °C to room temp. 1 h, 73% over two steps; h) [Ru]-**II** (30 mol-%), **17** (3 equiv.), CH_2Cl_2, room temp., 72 h, 32%; i) Pd/C 5% (5 mol-% Pd), EtOAc, room temp., 10 h, 96%. TESCl = triethylsilyl chloride, NMO = *N*-methyl-morpholine *N*-oxide.

(20 mol-%) in refluxing toluene to produce macrolactone **22** in 39% yield. Finally, after removal of the last protecting group at C9 by using HF·pyridine complex in THF, (+)-migrastatin (**1**) was isolated in 62% yield (Scheme 6). All the spectroscopic (^1H, ^{13}C NMR), HRMS, and optical rotation data of our synthetic (+)-migrastatin matched those reported in the literature.[3]

Conclusions

In conclusion, migrastatin was synthesized in 27 steps from the commercially available (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**2**). Synthetic highlights include the



Scheme 6. Completion of the total synthesis of migrastatin (**1**). Reagents and conditions: a) THF/H_2O/AcOH (1:1:3), 36 h, room temp., 80%; b) mixed anhydride **19** (3 equiv.), pyridine (4 equiv.), toluene, 48 h, room temp., 74%; c) NH_4F (30 equiv.), MeOH, room temp., 24 h, 81%; d) Dess–Martin periodinane (1.5 equiv.), CH_2Cl_2, 0 °C to room temp. 3 h; e) Zn, $PbCl_2$ (cat), CH_2I_2, $Ti(OiPr)_4$, THF, room temp., 54% yield for the last two steps; f) [Ru]-**I** (20 mol-%), toluene (c = 0.5·10^{-3} M), reflux, 0.3 h, 39%; g) HF·pyr complex, THF, room temp., 24 h, 62% yield.

use of versatile reactions such as a *syn*,*syn*-stereoselective crotylstannylation to control the stereogenic centers at C9 and C10, a crotyltitanation to control the stereogenic centers at C13 and C14, two ruthenium-catalyzed ring-closing methatheses, one to control the (*Z*)-trisubstituted double bond at C11–C12, one to establish the macrolactone core, and a ruthenium-catalyzed cross-metathesis to install the glutarimide side chain. These flexible synthetic methods should allow access to a variety of migrastatin analogues for biological evaluation.

Experimental Section

Selected analytical data for compounds **6**, **14**, and **1**.

6: M.p. 110–115 °C. $[\alpha]_D^{20}$ = –49.8 (c = 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H), 7.47–7.36 (m, 6 H), 6.60 (dd, J = 6.1 and 1.4 Hz, 1 H), 4.54 (dd, J = 7.6 and 1.4 Hz, 1 H), 3.84 (dd, J = 11.5 and 4.0 Hz, 1 H), 3.68 (dd, J = 11.5 and 4.0 Hz, 1 H), 3.41 (s, 3 H), 3.37 (dt, J = 8.0 and 4.0 Hz, 1 H), 2.42 (m, 1 H), 1.90 (s, 3 H), 1.05 (s, 9 H), 0.97 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 145.1, 135.8, 135.6, 133.2, 132.9, 129.9, 127.9, 127.8, 127.3 ppm. HRMS (ESI): calcd. for $C_{26}H_{34}O_4SiNa$ [M + Na]$^+$ 461.2124; found 461.2107.

14: $[\alpha]_D^{20}$ = –6.6 (c = 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (br. s, 1 NH), 7.73 (m, 4 H), 7.41 (m, 6 H), 6.69 (dt, J = 15.5 and 6.4 Hz, 1 H), 6.25 (d, J = 15.8 Hz, 1 H), 5.37 (d, J = 10.3 Hz, 1 H), 4.54 (d, J = 9.5 Hz, 1 H), 3.78 (dd, J = 11.0 and 4.6 Hz, 1 H), 3.67 (dd, J = 11.1 and 5.9 Hz, 1 H), 3.48 (d, J = 7.4 Hz, 1 H), 3.27 (s, 3 H), 3.16 (m, 1 H), 3.01 (m, 1 H), 2.65–2.79 (m, 3 H), 2.24–2.38 (m, 5 H), 1.66 (s, 3 H), 1.07 (s, 9 H), 0.90 (s, 9 H), 0.88 (d, J = 7.7 Hz, 3 H), 0.78–0.85 (m, 12 H), 0.45 (q, J = 8 Hz, 6 H), 0.03 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 171.5, 140.1, 135.8, 135.8, 134.3, 134.1, 133.6, 133.5, 132.4, 129.7, 127.8, 127.8, 85.4, 76.9, 72.9, 64.1, 59.1, 47.9, 37.5, 37.5, 37.4, 33.1, 29.9, 27.0, 26.2, 19.2, 18.5, 17.6, 14.3, 14.1, 6.9, 4.7, –3.8, –4.5 ppm. HRMS (ESI): calcd. for $C_{49}H_{79}O_7NSi_3Na$ [M + Na]$^+$ 900.5062; found 900.5040.

1: $[\alpha]_D^{25}$ = +11.1 (c = 0.05, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br. s, 1 NH), 6.50 (m, 1 H), 5.65 (dd, J = 10.4 and 1.7 Hz, 1 H), 5.59 (dd, J = 16.0 and 1.4 Hz, 1 H), 5.47–5.56 (m, 1 H), 5.24 (dd, J = 15.5 and 5.0 Hz, 1 H), 5.09 (d, J = 10.0 Hz, 1 H), 3.47 (dd, J = 9.0 and 5.0 Hz, 1 H), 3.30 (s, 3 H), 3.05 (dd, J = 8.6 and 2 Hz, 1 H), 2.87–3.02 (m, 2 H), 2.66–2.74 (m, 2 H), 2.50 (app t, J = 7.0 Hz, 2 H), 2.38–2.47 (m, 2 H), 2.07–2.30 (m, 5 H), 1.86 (d, J = 1.2 Hz, 3 H), 1.50–1.70 (m, 2 H), 1.30–1.39 (m, 2 H), 1.12 (d, J = 7.3 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 171.8, 164.0, 150.0, 133.2, 131.3, 130.7, 128.2, 122.3, 82.6, 78.1, 77.3, 57.0, 51.4, 40.1, 37.8, 37.8, 34.3, 32.1, 31.2, 30.5, 30.2, 26.1, 20.3, 13.5 ppm. HRMS (DCI$^+$, NH_3): calcd. for $C_{27}H_{43}O_7N_2$ [M + NH_4]$^+$ 507.3070; found 507.3069.

Acknowledgments

We wish to thank Dr. Fisher and Dr. Trimmer, from Materia (US) for a generous gift of Grubbs and Hoveyda–Grubbs catalysts.

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[6] On the basis of the ^{1}H NMR spectra of the crude reaction mixture.

[7] Conversion was monitored by GC/MS. The catalyst [Ru]-**I** was added in six portions over 144 h.

[8] The homodimer of diene **5** was also isolated in 5% yield.

[9] The corresponding saturated diol was also isolated in 10% yield.

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[14] Enone **13** was recovered with 40% yield. The catalyst [Ru]-**II** and compound **17** were added in three portions over 72 h. Yields for this reaction range from 27% to 50%.
[15] When the reaction was performed under microwave irradiation, the yield of this CM did not increase. See: F. C. Bargiggia, W. V. Murray, *J. Org. Chem.* **2005**, *70*, 9636–9639.
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Received: August 29, 2006
Published Online: September 18, 2006

