Enantioselective Synthesis of Medium-Sized Ring-Bridged Oxabicycles by Ring-Closing Metathesis

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Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday

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A flexible strategy is described for the enantioselective construction of both optical antipodes of the oxabicyclo[4.2.1]-, [5.2.1]-, and [6.2.1]-alkenes by a ring-closing metathesis reaction of the suitable 2,5-cis-dialkenyltetrahydrofurane derivatives.

Introduction

Ring-closing metathesis (RCM) catalysed by carbene transition metal complexes[1,2] has become one of the most popular synthetic methods for the formation of a C–C bond. Commercially available Grubbs' catalyst[3] is widely used because of its tolerance of a wide range of functional groups and its easy bench handling. While the RCM reaction has found a wide use in the construction of medium ring-sized carbo- and heterocycles, its use in the construction of medium-sized bridged compounds is scarce.[4] In this paper we report on a flexible strategy for the enantioselective synthesis of the medium-sized bridged oxabicyclo[n-2.1]-alkenes V and ent-V (n = 4, 5, 6) (Scheme 1) by an RCM reaction of the conformationally constrained dienes IV and ent-IV, respectively. Bridged oxabicyclic compounds are not only a synthetic target in their own right, but also because of their use as templates and building blocks in organic synthesis.[5] In addition, the bridged 11-oxabicyclo[6.2.1]-undecane is a central and common sub-structural motif of the cephalonoids,[6] a pharmacologically important family of marine metabolites with a wide spectrum of biological activity.

Results and Discussion

The strategy is outlined in Scheme 1. We proposed to build the enantiomeric medium-sized bridged oxabicycles V and ent-V through the ring-closing metathesis reactions of dienes IV and ent-IV, respectively. The 2,5-cis geometry of the alkyl chains must bring the diene termini into close proximity and so reduce the entropic cost associated with the ring-closing process. The exo-directed allylation[7] of the bicyclic acetals II and ent-II should permit access to olefins III and ent-III, respectively, as diastereomerically pure compounds. The bicyclic acetals II is obtained from diol I through the Suárez protocol,[8,9] which relocates the original anomic position of β-mannose to the new one created by β-fragmentation at the anomic position, and traps the intermediate by the secondary hydroxy group placed on the chain (α-marked oxygen atom). Finally, the enantio-

Scheme 1. Retrosynthetic analysis for the synthesis of both antipodes of medium-sized bridged oxabicyclo[n-2.1]-alkenes V and ent-V (n = 1, 2, 3)
eric acetal ent-II is directly obtained from d-xylene by simple protecting groups manipulation.

**Synthesis of the Dienes**

Epoxide 11\(^{11}\) (Scheme 2) was treated with vinylmagnesium chloride in the presence of CuI\(^{12}\) to give alcohol 2 in 98% yield. Protection and oxidative hydroboration gave the alcohol 4 in 99% yield. Hydrolysis and regioselective protection of the primary hydroxyl group as its pivaloyl ester gave the alcohol 6 in 92% yield.

![Scheme 2](image)

Scheme 2. Reagents and conditions: (a) CH\(_2\)CH\(_2\)MgCl/CuI, THF, room temp., 1 h; (b) NaOAc/H\(_2\)O, room temp., 0.5 h, 90%; (d) KOH, MeOH, 15 min, room temp.; (e) PhCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0 °C, 1 h, 92%; (f) DDQ, H\(_2\)O/CH\(_2\)Cl\(_2\), room temp., 16 h, 91%; (g) Pd(II), 1°, CH\(_2\)Cl\(_2\), 6 h, 70%; (h) Na\(_2\)SO\(_4\)/MeOH, room temp., 10 min, 99%; (i) TBDMSCl, imidazole, DMF, 60 °C, 16 h, 91%. (j) (CH\(_2\)\(_3\))\(_3\)SiCH\(_2\)CH\(_2\)BF\(_3\)-EtO, CH\(_2\)Cl\(_2\), room temp., 6 h, 85%; (k) TBDMSCl, imidazole, DMF, 60 °C, 16 h, 90%; (l) DIBAL, CH\(_2\)Cl\(_2\), −78 °C, 1 h, 95%.

Deprotection at the anomic position by reaction with DDQ gave the diol 7, which was easily transformed into the bicyclic acetal 8 by the Suárez protocol. Therefore, treatment of lactol 7 with iodobenzene and iodine resulted in oxidative β-fragmentation of the anomic oxygen-centred radical, affording the formyl derivative 8 in 70% yield. Basic hydrolysis and reprotection of the hydroxyl group as its tert-butylidemethylsilyl ether gave the acetal 10 in a yield of 91%. The *exo*-directed alllylation\(^{17}\) of this bicyclic acetal gave the alkene 11 as a unique diastereomer in 85% yield. Protection of the secondary hydroxy group as its tert-butylidemethylsilyl ether followed by DIBAL deprotection of the primary pivaloyl ester gave the alcohol 13 in a yield of 86%. Synthetic manipulation of the primary hydroxy group of 13 allowed the installation of the required second alkyl chain (Scheme 3). Therefore, Grieco elimination of the primary hydroxy group gave diene 14 in a 75% yield. Swern oxidation, followed by a Wittig olefination efficiently transformed 13 into the diene 15 (70%). Finally, mesylate formation, cyanide displacement, DIBAL reduction of the cyanide group to the imine, followed by hydrolysis to the aldehyde, and Wittig olefination afforded diene 18 in a 40% overall yield.

**Ring-Closing Metathesis Reactions**

Initial metathesis reactions were carried out with the diene 14 to obtain the 9-oxabicyclo[4.2.1]non-3-ene 23.
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Table 1. Conditions for ring-closing metathesis of dienes 14, 15, ent-15, and 18

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[10] In all cases 20 mol % of [P(2'-ri)₃RuCHP]Cl₂ was used. [11] (A) 0.02 M in diene. (B) 0.003 M. (C) 0.02 M and the catalyst added in two portions at eight-hour intervals. [11] RSM = Recovered Starting Material.

(Scheme 5). After attempting to modify several experimental conditions including solvent, catalyst charge,[13] and temperature (Table 1, Entries 1–5), refluxing benzene (0.02 M) with a 20 mol % of Grubbs’ catalyst charge were found to be the best conditions, affording 24 in 64% yield. Remarkably, in spite of the known difficulty in forming eight-membered rings by this reaction,[14–16] dienes 15 and ent-15 gave the 10-oxabicyclo[5.2.1]dec-3-enes 24 and ent-24 in a 45% and 40% yield, respectively (Entries 9 and 12). Unfortunately, the efficiency of the reaction could not be improved by changes in the experimental conditions (Entries 6–11).

Diene 18 also underwent the RCM reaction with acceptable efficiency, affording the (15S,8R,9S,10S)-9,10-di-tert-butoxy-11-oxabicyclo[6.2.1]undec-3-ene (25) in 53% yield (Entries 13–15). Although this 53% yield is susceptible to improvement by the use of other catalysts,[14] this is still good enough for synthetic use.

Conclusion

Some features of this methodology are noteworthy: Firstly, it opens a synthetic access to the medium-sized oxabicyclo[4.2.1]non-3-ene, [5.2.1]dec-3-ene, and [6.2.1]undec-3-ene in both their enantiomerically pure forms and with a moderate to good yield; secondly, dienes 14, 15, and 18 and their enantiomers ent-14, ent-15, and ent-18 are easily synthesised from cheap and commercially available carbohydrates by means of standard reactions and in a highly chemo- and stereoselective mode; thirdly, the synthetic protocol admits a wide functional group presence on both alkynyl chains, which is very important in order to apply this methodology to the synthesis of more elaborated targets; and finally, the RCM reactions are carried out with the aid of a commercial and bench stable Grubbs’ catalyst with moderate to good efficiency. It is hoped that the new family of more reactive Grubbs’ catalysts[15] (still not commercially available) could improve the chemical efficiency of these cyclizations.

Experimental Section

General Remarks: Melting points are uncorrected and were determined in a Reichert Thermovar apparatus. 1H NMR and 13C NMR spectra of CDCl₃ solutions were recorded either at 200 and 50 MHz or at 500 and 125 MHz (Bruker AC 200 and AMX2-500, respectively). FT-IR spectra were measured in chloroform solutions using a Shimadzu IR-408 spectrophotometer. Mass spectra (low resolution) (EI/Cl) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyser. Optical rotations were determined at room temperature with a Perkin-Elmer 241 polarimeter and are referenced to the D-line of sodium. Analytical thin-layer chromatography plates used were E. Merck Kieselgel UV-active silica gel (Kieselgel 60 F254) on aluminium. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated in the text. Tetrahydrofuran, benzene, and toluene were distilled from sodium metal benzophenone ketyl. Dichloromethane, dimethyl sulfoxide, dimethylformamide, and triethylamine were distilled from CaH₂.


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Bis(tricyclohexylphosphine)benzylidenen ruthenium(IV) dichloride (Grubbs' catalyst) was prepared from Strem Chemicals, and used under nitrogen with standard Schlenk techniques.

4-Methoxybenzyl 6,7,8-TrIDEOxy-3,2-O-(1-methylethylidene)-α-D-mannono-0ct-7-enofuranoside (2): In an oven-dried round-bottomed flask was placed Cu (1.29 g, 6.76 mmol) and the flask was purged with nitrogen. Dry THF (20 mL) was added and the suspension was cooled to −30 °C. Vinylogous chloride (1.7 mL in THF) (9 mL, 13.6 mmol) was added and the mixture was stirred at −30 °C for 15 min. Then, epoxide (2.18 g, 6.8 mmol) in dry THF (40 mL) was added via cannula and the mixture was slowly warmed from −30 °C to −10 °C during 2 h. Aqueous saturated NH₄Cl was added to destroy the reagent excess and the mixture was transferred to a decantation funnel then washed with anhydrous diethyl ether. The organic phase was washed with H₂O (3×), 1 N HCl (3×), aqueous sodium bicarbonate (3×), and aqueous saturated NaCl (3×), dried with Na₂SO₄, filtered, and concentrated to give a gum residue. Flash chromatography (eluent gradient: ethyl acetate/hexanes from 2:8 to 4:6) gave pure 4 (yield 1.57 g, 33%); mp 248-249 °C (from Et₂O); [α]D = 60.7 (c = 0.26, CHCl₃); 1H NMR (200 MHz, CDCl₃): δ = 5.28 (m, 2 H), 4.83 (dd, δ = 7.0 Hz, 1 H), 4.51 (t, δ = 6.0 Hz, 2 H), 4.07 (q, δ = 6.0 Hz, 1 H), 3.83 (dd, δ = 7.0 Hz, 1 H), 3.79 (s, 3 H), 1.79 (s, 3 H), 0.81 (t, δ = 7.0 Hz, 3 H).

6.7-Dideoxy-8-O-(2,2-dimethylpropanoyl)-2,3-O-(1-methylethylidene)-α-D-mannono-octofuranoside (5): Alcohol 6 (2 g, 4.4 mmol) in CH₂Cl₂ (90 mL) and H₂O (4.5 mL) was vigorously stirred with DDQ (1.5 g, 6.6 mmol) at room temperature for 16 h. Aqueous saturated NaCl solution (1 mL) was added and the resulting mixture stirred for 15 min. Filtration through a pad of Celite and concentration gave a solid residue that was purified by flash chromatography (eluent gradient: ethyl acetate/hexanes from 2:8 to 6:4) to give pure hemiacetal 7 (yield 1.33 g, 91%). M.p. 83.7-84.7 °C (ethyl acetate/hexane). [α]D = 7.98 (c = 0.038, CHCl₃).

1H NMR (200 MHz, CDCl₃): δ = 5.37 (s, 1 H), 4.69 (dd, δ = 6.0 Hz, 1 H), 4.57 (d, δ = 6.0 Hz, 1 H), 4.07 (t, δ = 6.0 Hz, 2 H), 3.97 (m, 2 H), 1.71 (m, 4 H), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.19 (s, 3 H).

13C NMR (50 MHz, CDCl₃): δ = 178.6, 112.3, 105.0, 85.8, 82.9, 79.1, 69.7, 64.0, 38.6, 28.6, 26.7 (C 2), 25.8, 24.6, 24.4. LMRSM (EI, m/z): 542 (40%, [M]+), 437 (3.3), 315 (0.2), 299 (0.3), 273 (6.4), 258 (1.4), 249 (2.8), 227 (1.8), 183 (4.5), 171 (3.6), 163 (1.8), 143 (1.6), 137 (2.1), 125 (10), 121 (100), 85 (7.2), 71 (10.3), 57 (32). C₇H₁₆O₆ calculated: C 63.70, H 8.02; found C 63.80, H 8.02.
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Enantioselective Synthesis of Medium-Sized Ring-Bridged Oxabicycles

5,6-Dideoxy-7-O-(2,2-dimethylpropyl)-1,2-O-(1-methylhydroxymethyl)-d-threo-hexitol (13): Alcohol (70 mg, 0.19 mmol) in dry THF (2 mL) was stirred with sodium hydride (6.0 mmol) and DIBAL (2 mL) at 0°C for 1 h. After cooling to 0°C, the mixture was cooled to -78°C for 1 h and quenched with 1 M NaOH (5 mL). The reaction mixture was then diluted with EtOAc (50 mL) and washed with water (20 mL), brine (20 mL), and then dried over MgSO4. The mixture was filtered and evaporated to yield an oily residue. The residue was purified by flash chromatography (eluent gradient: hexane/acetone 1:1) to give 12 (yield 46 mg, 0.14 mmol) as a white solid. 1H NMR (500 MHz, CDCl3): δ = 5.49 (s, 2 H); 3.77 (d, J = 8.0 Hz, 2 H); 2.90 (t, J = 7.0 Hz, 2 H); 2.28 (t, J = 7.0 Hz, 2 H); 1.96 (s, 3 H); 1.58 (s, 3 H). 13C NMR (125 MHz, CDCl3): δ = 173.1, 159.5, 134.4, 117.0, 82.6, 81.4, 76.8, 64.3, 38.6, 27.1, 20.5, 25.7, 20.9, 19.0, 18.0, 14.1. LRMSE: m/z (%) = 341 (2.4) [M+H]+. 250 (17.3), 230 (12.5), 216 (7.5), 171 (2.5), 159 (2.1), 75 (1.5), 57 (3.1), C21H29O6Si: Calcd. C 59.8, H 6.7; Found C 59.2, H 6.7.

3-0-(tert-Butyldimethylsilyl)-5,6-dideoxy-7-O-(2,2-dimethylpropyl)-1,2-O-(1-methylhydroxymethyl)-d-threo-hexitol (10): Alcohol (90 mg, 0.28 mmol) in dry THF (3 mL) was stirred with sodium hydride (6.0 mmol) and DIBAL (3 mL) at 0°C for 1 h. After cooling to 0°C, the mixture was cooled to -78°C for 1 h and quenched with 1 M NaOH (5 mL). The reaction mixture was then diluted with EtOAc (50 mL) and washed with water (20 mL), brine (20 mL), and then dried over MgSO4. The mixture was filtered and evaporated to yield an oily residue. The residue was purified by flash chromatography (eluent gradient: hexane/acetone 1:1) to give 11 (yield 53 mg, 0.15 mmol) as a white solid. 1H NMR (500 MHz, CDCl3): δ = 5.49 (s, 2 H); 3.77 (d, J = 8.0 Hz, 2 H); 2.90 (t, J = 7.0 Hz, 2 H); 2.28 (t, J = 7.0 Hz, 2 H); 1.96 (s, 3 H); 1.58 (s, 3 H). 13C NMR (125 MHz, CDCl3): δ = 173.1, 159.5, 134.4, 117.0, 82.6, 81.4, 76.8, 64.3, 38.6, 27.1, 20.5, 25.7, 20.9, 19.0, 18.0, 14.1. LRMSE: m/z (%) = 341 (2.4) [M+H]+. 250 (17.3), 230 (12.5), 216 (7.5), 171 (2.5), 159 (2.1), 75 (1.5), 57 (3.1), C21H29O6Si: Calcd. C 59.8, H 6.7; Found C 59.2, H 6.7.

(7S)-7- Allyl-4,7-anhydro-5,6-bis-O-(tert-butylidemethylsilyl)-1,2,3-trideoxyo-(2R,3S)-arabinohexo-1-entiol (14): A solution of 12 (358 mg, 0.99 mmol) in dry CH2Cl2 (5 mL) was cooled to -78°C and DIBAL (2 mL) was added. After cooling to 0°C for 1 h, the mixture was cooled to -78°C for 1 h and quenched with 1 M NaOH (5 mL). The reaction mixture was then diluted with EtOAc (50 mL) and washed with water (20 mL), brine (20 mL), and then dried over MgSO4. The mixture was filtered and evaporated to yield an oily residue. The residue was purified by flash chromatography (eluent gradient: hexane/acetone 1:1) to give 13 (yield 316 mg, 0.92 mmol) as a yellow solid. 1H NMR (500 MHz, CDCl3): δ = 5.49 (s, 2 H); 3.77 (d, J = 8.0 Hz, 2 H); 2.90 (t, J = 7.0 Hz, 2 H); 2.28 (t, J = 7.0 Hz, 2 H); 1.96 (s, 3 H); 1.58 (s, 3 H). 13C NMR (125 MHz, CDCl3): δ = 173.1, 159.5, 134.4, 117.0, 82.6, 81.4, 76.8, 64.3, 38.6, 27.1, 20.5, 25.7, 20.9, 19.0, 18.0, 14.1. LRMSE: m/z (%) = 341 (2.4) [M+H]+. 250 (17.3), 230 (12.5), 216 (7.5), 171 (2.5), 159 (2.1), 75 (1.5), 57 (3.1), C21H29O6Si: Calcd. C 59.8, H 6.7; Found C 59.2, H 6.7.

(7R)-4,7-Anhydro-7-(3-butenyl)-5,6-bis-O-(tert-butyldimethylsilyl)-1,2,3-trIDEOxy-4-arabino-hept-1-enitol (15): DMSO (0.07 mL, 0.96 mmol) was added dropwise to a solution of oxalyl chloride (0.04 mL, 0.48 mmol) in CH₂Cl₂ (2 mL) at −78 °C, and the resulting mixture was stirred for 20 min. A solution of alcohol 13 (see above) (104 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was added via cannula to the reaction mixture and the resulting mixture was stirred for 20 min at this temperature. Then, Et₃N (0.2 mL, 1.44 mmol) was added and the resulting mixture stirred for 10 min before being warmed to room temperature. The mixture was poured into H₂O and the two layers were separated. The aqueous layer was extracted with diethyl ether (2 × 2 mL) and the combined organic layers were dried with Na₂SO₄. The solvent was removed under reduced pressure, and the crude aldehyde was used in the next reaction without further purification. — A suspension of methyltriphosphonium iodide (126 mg, 0.3 mmol) in THF (1.5 mL) was treated at 0 °C with nBuLi (0.2 mL, 3.0 mmol, 1.6 M in hexane). After stirring for 1 h at this temperature, the aldehyde (the residue from the previous step) was treated with aqueous saturated NH₄Cl solution (1 mL) and extracted with diethyl ether (2 × 3 mL). The organic layer was dried with Na₂SO₄, the solvent was removed under reduced pressure and the residue purified by flash chromatography (n-hexane/benzene: 7:3) to give 16 (yield 72 mg, 70% for the two steps) as a colourless oil. [α]D = +22.5 (c = 0.14, CHCl₃). IR (CHCl₃): ν = 3018, 2986, 2930, 2838, 1640, 1471, 1463, 1258 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 5.8 (m, 4 H), 5.0 (m, 2 H), 3.91 (dd, 1 H, J = 9, 8 and 3 Hz), 3.83 (s, 1 H), 3.75 (d, J = 3.0 Hz), 3.7 (d, J = 7.0 Hz, 1 H, 2.4 (m, 1 H), 2.3 (m, 1 H), 2.16 (m, 1 H), 2.07 (m, 1 H), 1.73 (m, 1 H), 1.62 (m, 1 H), 1.09 (s, 9 H), 0.86 (s, 3 H), 0.05 (s, 3 H), 0.13 (s, 3 H), 0.04 (s, 3 H). ¹³C NMR (50 MHz, CDCl₃): δ = 138.4, 135.2, 116.7, 114.2, 86.0, 89.0 (2 C), 79.2, 38.6, 30.5, 28.1, 25.7 (3 C), 25.5 (3 C), 17.9, 17.7, −4.3, −4.45, −4.54, −5.1. HRMS (EI): calc. for C₉H₁₆NO₃Si: M⁺ = 319.0899; found 319.0857.

(7S)-4,7-Anhydro-5,6-bis-O-(tert-butyldimethylsilyl)-7-(3-cyanopropyl)-1,2,3-trIDEOxy-4-arabino-hept-1-enitol (17): To a solution of alcohol 13 (207 mg, 0.48 mmol) in dry CH₂Cl₂ (3 mL) was added dry Et₃N (0.33 mL, 2.4 mmol) and MsCl (0.07 mL, 0.96 mmol) and the resulting mixture was stirred at 0 °C for 30 min. More CH₂Cl₂ was added and the resulting solution was washed with 1 N HCl. The organic layer was dried with Na₂SO₄ and the solvent removed under reduced pressure. The crude residue 16 was dissolved in dry DMF (3 mL) and stirred at room temperature for 0.5 h. Then, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and the solution transferred to a 10 mL vial. A solution of nBuLi (1.6 M, 27.0 mL, 43.2 mmol, 0.95 M in hexane) was added via cannula and the mixture was stirred for 1 h at this temperature. The aldehyde (the residue from the previous step) was treated with aqueous saturated NH₄Cl solution (2 mL) and extracted with diethyl ether (2 × 4 mL). The organic layer was dried with Na₂SO₄, the solvent was removed under reduced pressure and the residue purified by flash chromatography (n-hexane/benzene: 7:3) to give 16 (yield 85 mg, 58% for the two steps) as a colourless oil. [α]D = −20.1 (c = 0.08, CHCl₃). IR (CHCl₃): ν = 3013, 2989, 2935, 2813, 2786, 1641, 1471, 1463, 1258 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 5.8 (m, 4 H), 5.0 (m, 2 H), 3.91 (dd, 1 H, J = 9, 8 and 3 Hz), 3.83 (s, 1 H), 3.75 (d, J = 3.0 Hz), 3.7 (d, J = 7.0 Hz, 1 H), 2.4 (m, 1 H), 2.1 (m, 1 H), 2.07 (m, 1 H), 1.73 (m, 1 H), 1.62 (m, 1 H), 1.09 (s, 9 H), 0.86 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H). ¹³C NMR (50 MHz, CDCl₃): δ = 138.4, 135.2, 116.7, 114.2, 86.0, 89.0 (2 C), 79.2, 38.6, 30.5, 28.1, 25.7 (3 C), 25.5 (3 C), 17.9, 17.7, −4.3, −4.45, −4.54, −5.1. HRMS (EI): calc. for C₉H₁₆NO₃Si: M⁺ = 319.0899; found 319.0857.
organic phase decanted. The aqueous phase was extracted with more CH$_2$Cl$_2$ and the combined organic phases were washed with aqueous saturated NaCl solution, dried with Na$_2$SO$_4$ and concentrated to give an oily residue. Flash chromatography (elucent gradient: ethyl acetate/benzene from 5:95 to 1:1) gave the pure alcohol (yield 515 mg, 55%) which was transformed into the diene end-15 ([$\delta_{D}]$ = $-19$ (c = 0.2, CHCl$_3$)) using the same procedure as in the case of 12 (see above).

**Synthesis of the Oxabicycles 23, 24, 25, and end-24.**

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**Method A:** To a solution of the corresponding dienes 14, 15, 18, and end-15 (0.23 mmol, 0.02 M) in dry degassed benzene was added the Grubbs' catalyst (20 mmol %). After stirring the reaction mixture for 16 h at reflux, the solvent was removed in vacuo and the residue was purified by flash chromatography (n-hexane/benzene: 7:3) to give the corresponding oxabicycles 23, 24, 25, and end-24, respectively.

**Method B:** The same as Method A, but using more dilute conditions (0.003 M in diene).

**Method C:** To a solution of the corresponding dienes (0.23 mmol, 0.02 M) in dry degassed benzene was added the Grubbs' catalyst (10 mmol %). After stirring the reaction mixture for 8 h at reflux, a second charge of catalyst was added (10 mmol %) and the mixture further heated under reflux for 8 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (n-hexane/benzene: 7:3) as in Method A.

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[6] For recent studies of asymmetric ring-closing metathesis, see:
[11] For synthesis of small bridged bicyclo-alkanes, see:
[18] We have recently completed an in-depth study of the template effect of this bicyclic acetal on the stereoselective synthesis of C-furanosides; F. Garcia-Tellado, P. Armás, J. J. Marrero-Tellado, Angew. Chem., Int. Ed. Engl. 2000, 39, 2727. For stereoselective alkylation of five-membered ring oxocarbenium ions, see:
[27] Although the reaction was initially described as a radical process, we have shown that the reaction is ionic in nature: P. Armás, F. García-Tellado, J. J. Marrero-Tellado, J. Robles, Tetrahedron Lett. 1997, 38, 8801.