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Regio- and stereoselective ring-opening dimerization–cross-coupling metathesis of 7-oxanorbornene derivatives

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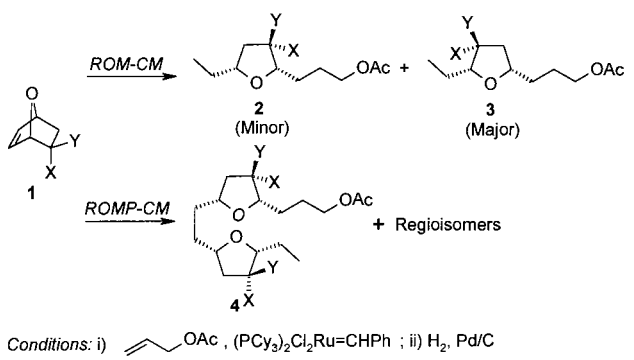
Abstract

A new metathesis-based route for the linking of two tetrahydrofuran moieties by an ethylene subunit has been developed. Treatment of an optically pure 2-substituted 7-oxanorborn-5-ene with Grubbs' ruthenium catalyst in the presence of allyl acetate afforded the product of two successive ring-opening metatheses and cross-metathesis in a highly regioselective fashion. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Metathesis; Tetrahydrofurans; Ruthenium; Dimerization; Regioselective synthesis

1. Introduction

The ring-opening metathesis (ROM) and cross-coupling metathesis (CM) of bicyclic olefins constitutes a powerful approach for the construction of highly functionalized cyclic organic molecules [1]. In particular, 7-oxanorbornenes are known to undergo ring-opening polymerization metathesis (ROMP) generating a variety of functional polymers [2], and the tandem ROM–CM of 2-substituted 7-oxanorbornene derivatives [3,4] has provided a new regio- and stereoselective entry into tri- and tetrasubstitued tetrahydrofurans (Scheme 1). The regioselectivity of this reaction was such that the larger alkyl chain of the major product was located on the less hindered side of the tetrahydrofuran ring.



Scheme 1.

At this point we speculated that the combination of ROMP and ROM–CM procedures could be the basis of a new method for linking two tetrahydrofuran rings by an ethylene chain, by truncating the ROMP with a CM process in a regioselective fashion. It should be pointed out that the carbon backbone of certain higher carbohydrates is constituted of this type of structure [5,6]. In this way, we have chosen the readily available, optically pure (1*R*,4*R*)-2,2-ethylenedioxy-7-oxabicyclo[2.2.1]hept-5-ene (**5**) [7] as the model compound in order to study the feasibility of this approach.

2. Results and discussion

The reaction of dilute solutions of compound **5** in CH_2Cl_2 with an equimolecular amount of alkene **6** in

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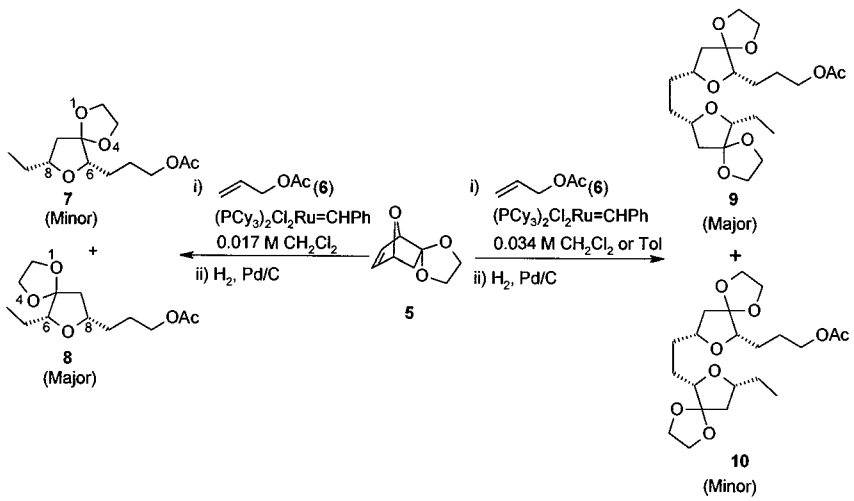


Scheme 2.

Table 1
Reaction of **5** with **6** in the presence of [Ru] [a]

Entry	Molar ratio **5**:**6**	Solvent (M)	[Ru] [b]	T (°C)	**7**, **8** (%) [c]	**9**, **10** (%) [c]
1	1:1	CH_2Cl_2 (0.017)	0.06	25	80	10
2	1:1	CH_2Cl_2 (0.034)	0.06	25	35	45
3	1:1	CH_2Cl_2 (0.034)	0.06	40	25	40
4	1:1	Toluene (0.034)	0.06	25	14	12
5	1:1	THF (0.034)	0.06	25	35	20
6	2:1	CH_2Cl_2 (0.017)	0.06	25	20	10
7	1:1	CH_2Cl_2 (0.034)	0.12	25	25	60

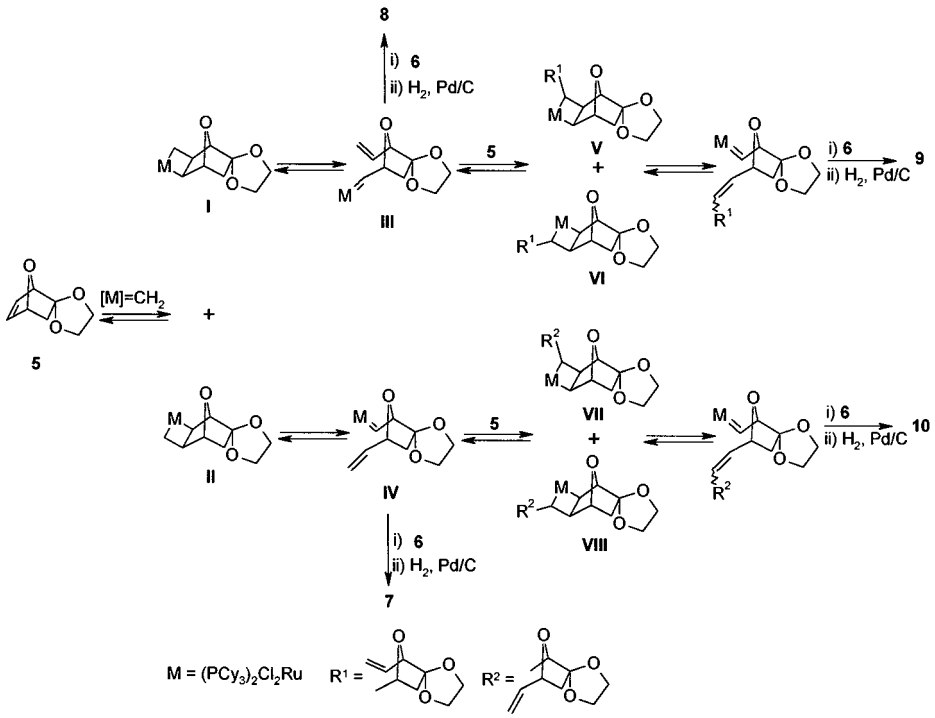
[a] [Ru] = $(Cy_3P)_2Cl_2Ru$=CHPh.
[b] Mole of [Ru] per mole of **5**.
[c] Isolated combined yield.

the presence of Grubbs' ruthenium catalyst [8] (6% mol) afforded [4], after catalytic hydrogenation (H_2, Pd/C, 5%, MeOH), the tetrahydrofuran derivatives **7** and **8** in a 21:79 ratio (80% combined yield). On the other hand, it is well known that ring-opening polymerization is favored in concentrated solutions [1]. Therefore, when the ROM–CM reaction of **5** was carried out in a more concentrated CH_2Cl_2 solution, the polymerization was truncated by the cross coupling of the carbene intermediates with alkene **6**, and the dimerization products **9** and **10** were isolated in a 94:6 ratio (45% combined yield) after hydrogenation of the reaction mixture (Scheme 2). The other two possible regioisomers were not detected in the crude reaction mixtures.

Different reaction conditions were tested in order to enhance the yield in dimers **9** and **10**. The results are given in Table 1.

The inspection of these data puts forward that, together with an increase in concentration (entry 2), an increase in the reaction temperature also favored the dimerization process (entry 3). Extensive polymerization was observed when the solvent was changed to toluene (entry 4) or THF (entry 5), and when the reaction was carried out only with 0.5 equivalents of alkene 6 (entry 6). The best result was obtained by increasing the amount of Grubbs' catalyst in a 0.034 M CH_2Cl_2 solution (entry 7). Compounds **9** and **10** were isolated in a 94:6 ratio in all cases.

In order to account for the stereoselectivity in the ROM–CM dimerization process, the steric effects in the cycloaddition of the different carbene species must be considered [9] (Scheme 3). Thus, according to the mechanism proposed by Chauvin [10], the cycloaddition of the propagating species $(Cy_3P)_2Cl_2Ru$=CH_2 to the *exo* face of the C=C bond of the bicyclic alkene **5** should afford the fused metallacyclobutane intermediates **I** and **II** in a rate and product determining step, although all reactions involved are reversible to a greater or lesser extent [11]. Cycloreversion of **I** and **II** leads to ring opening, with the formation of the new carbene species **III** and **IV**. Steric interactions in the cyclometallation step between the bulky metal moiety and the dioxolane ring in **II** may explain the majoritary formation of **8** in the cross-coupling reaction with alkene **6**.



Scheme 3.

However, the cycloaddition of **III** and **IV** to the acyclic alkene **6** should be competitive with their cross-coupling with another molecule of the starting material **5**. In this case, the steric interaction between the dioxolane ring and the bulky tetrahydrofuran unit (R^1 or R^2) introduced in the first step is dominant, and may overwhelm the steric interaction between the dioxolane ring with the metal moiety, thus favoring the formation of **9** from intermediate **VI**, and formation of **10** from intermediate **VIII**. This result highlights the delicate balance of steric interactions of the different carbene species in the outcome of the ring-opening and cross-coupling metathesis.

The structural assignment of compounds **9** and **10** was based on their H,H-COSY spectrum and in the comparison of the MS data with those of the monomers **7** and **8**. Thus, the terminal CH_3 of **9** ($\delta = 0.98$ ppm, t, $^3J = 7$ Hz) correlated with one CH_2 group ($\delta = 1.55$ ppm, m) which in turn correlated with the hydrogen atom at C6 ($\delta = 3.63$ ppm, dd, $^3J = 7.8$, 5.2 Hz). Similarly, the terminal CH_3 of **10** ($\delta = 0.92$ ppm, t, $^3J = 7$ Hz) correlated with one CH_2 group ($\delta = 1.57$ ppm, m) which in turn correlated with the hydrogen atom at C8 ($\delta = 3.82$–3.98 ppm, m).

The MS spectrum of monomer **7** ($M = 258$) showed the loss of the ethyl chain at carbon C8 of the tetrahydrofuran unit[4] ($m/z = 229$), whereas compound **8** ($M = 258$) lost the $(CH_2)_3OAc$ chain at carbon C8 ($m/z = 157$). Only the fragmentation of the tetrahydrofuran ring at the C5–C6 and O–C8 bonds was observed either for **7** ($m/z = 128$) and **8** ($m/z = 200$), and the loss of the chains at C6 was not observed either in **7** ($m/z = 157$, M–$(CH_2)_3OAc$) or **8** ($m/z = 229$, M–CH_2CH_3).

A similar fragmentation pattern was found in the MS spectra of **9** and **10** ($M = 414$). Thus, the MS spectrum of **9** evidenced the loss of the chains at carbons C8 of each tetrahydrofuran subunits[4] was observed ($m/z =$ 229 and 157) together with the aforementioned tetrahydrofuran C5–C6/O–C8 ring fragmentation ($m/z = 284$ and 356), and the loss of CH_2CH_3 ($m/z = 385$) or $(CH_2)_3OAc$ ($m/z = 313$) were not observed. In analogous fashion, the MS spectrum of **10** ($M = 414$) showed the loss of the chain at carbons C8 of one of the tetrahydrofuran subunits ($m/z = 229$) and the C5–C6/O–C8 ring fragmentation of the other tetrahydrofuran subunit ($m/z = 128$).

In conclusion, a new metathesis-based route for the linking of two tetrahydrofuran moieties by an ethylene subunit starting from 7-oxanorbornene derivatives has been developed. Functionalization of the C=C bonds of the metathesis products different from hydrogenation may constitute a new entry into higher carbosugars.

3. Experimental

Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV and vainilline solution. Flash

[4] Numbering refers to the 1,4,7-trioxa-spiro[4.4]nonane skeleton. See Scheme 2.

column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. ^1H and ^{13}C NMR spectra were recorded at 300 and 50.5 MHz in $CDCl_3$ solutions. GC was carried out on a VA-5 column (30 m × 0.25 mm, film = 0.25 μm) at 190°C. MS was carried out at 70 eV.

3.1. Ring-opening and cross coupling metathesis of compounds **5** with alkene **6**

3.1.1. General procedure

To a solution of **5** (0.46 mmol) and alkene **6** (0.46 mmol, Table 1, entries 1–5 and 7, or 0.23 mmol, entry 6) in anhydrous CH_2Cl_2 (20 ml, Table 1, entries 1 and 6, or 10 ml, Table 1, entries 2, 3 and 7), toluene (10 ml, Table 1, entry 4) or THF (10 ml, Table 1, entry 5) was added $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.027 mmol, Table 1, entries 1–6, or 0.055 mmol, Table 1, entry 7) dissolved in the corresponding solvent (see Table 1) (6 ml, entries 1 and 6 or 3 ml, entries 2–5 and 7). The reaction mixture was stirred at the appropriate temperature (see Table 1) for 6 h. After conversion was complete (TLC monitoring), the solvent was removed under reduced pressure. The reaction mixture was filtered through a pad of silica gel, which was washed with a mixture of hexane–ethyl acetate = 3:2. After removal of the solvent under reduced pressure, the crude reaction mixture was dissolved in MeOH (5 ml), 5% Pd on charcoal (7 mg) was added and the mixture was hydrogenated at 50 PSI for 5 h. Filtration of the catalyst and evaporation of the solvent, afforded a brown oil which was purified by chromatography (silica gel, hexane–ethyl acetate = 3:2).

(6*R*,8*R*)-Acetic acid 3-(8-ethyl-1,4,7-trioxa-spiro[4.4]-non-6-yl)propyl ester (**7**) and (6*R*,8*R*)-acetic acid 3-(6-ethyl-1,4,7-trioxa-spiro[4.4]non-8-yl)propyl ester (**8**). (**7**:**8** = 21:79). Colorless oil. ^1H NMR (300 MHz, $CHCl_3$-*d*) δ 0.90 (t, $J = 7.5$ Hz, 3H, **7**), 0.98 (t, $J = 7.5$ Hz, 3H, **8**), 1.42–1.80 (m, 7H), 2.02 (s, 3H), 2.08 (dd, $J = 12.8$, 5.7 Hz, 1H), 3.55 (dd, $J = 7.6$, 5.1 Hz, 1H, **8**), 3.62 (dd, $J = 7.6$, 5.1 Hz, 1H, 7), 3.80–3.95 (m, 5H), 4.08 (m, 2H). ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 171.1, 116.1, 84.3 (**8**), 82.4 (**7**), 78.1 (**7**), 76.0 (**8**), 65.1, 64.4, 64.1, 43.3 (**8**), 42.9 (**7**), 31.8 (**8**), 28.3 (**7**), 26.7 (**7**), 25.3 (**7**), 25.0 (**8**), 23.2 (**8**), 20.9, 10.5. MS *m*/*z* (%) (**7**), 258 (11), 229 (14), 128 (18), 113 (22), 99 (100), 55 (22), 43 (34). MS *m*/*z* (%) (**8**), 258 (2), 157 (36), 141 (16), 113 (53), 99 (100), 55 (22), 43 (45). *Anal*. Found: C, 60.63; H, 8.70. Calc. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58%.

(6*R*,6′*R*,8*R*,8′*R*)-Acetic acid 3-{8-[2-(6-ethyl-1,4,7-trioxa-spiro[4.4]non-8-yl)-ethyl]-1,4,7-trioxa-spiro[4.4]-non-6-yl) propyl ester (**9**) and (6*R*,6′*R*,8*R*,8′*R*)-acetic acid 3-{8-[2-(8-ethyl-1,4,7-trioxa-spiro[4.4]non-6-yl)-ethyl]-1,4,7-trioxa-spiro[4.4]non-6-yl) propyl ester (**10**). (**9**:**10** = 94:6). Colorless oil. $[\alpha]_D = +23$ ($c = 0.5$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.6$ Hz, 3H, **10**), 0.98 (t, $J = 7.6$ Hz, 3H, **9**), 1.52–1.80 (m, 12H), 2.05 (s, 3H), 2.08–2.18 (m, 2H), 3.55 (dd, $J = 7.8$, 5.2 Hz, 1H), 3.63 (dd, $J = 7.8$, 5.2 Hz, 1H, **9**), 3.64 (dd, $J = 7.8$, 5.2 Hz, 1H, **10**), 3.82–3.98 (m, 9H), 4.05–4.15 (m, 3H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 171.3, 116.1, 115.9, 84.3, 82.5, 76.4, 76.1, 65.0, 64.6, 64.3, 64.2, 64.1, 43.5 (**10**), 43.3 (**9**), 43.2, 31.7 (**10**), 31.3 (**9**), 26.6, 26.5, 25.3, 23.3, 21.1, 10.6 (**9**), 9.9 (**10**) ppm. MS *m*/*z* (%) (**9**), 414 (23), 356 (5), 284 (6), 229 (14), 157 (24), 99 (100). MS *m*/*z* (%) (**10**), 414 (21), 229 (3), 128 (15), 99 (100). *Anal*. Found: C, 60.92; H, 8.42. Calc. for $C_{21}H_{34}O_8$: C, 60.85; H, 8.27%.

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