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Regioselective Ring-Opening and Cross-Coupling Metathesis of 2-Substituted 7-Oxanorbornenes. New Stereoselective Entry into Trisubstituted Tetrahydrofurans

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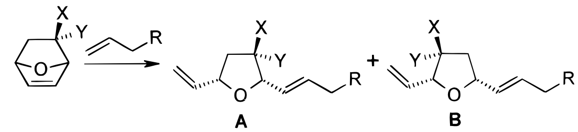
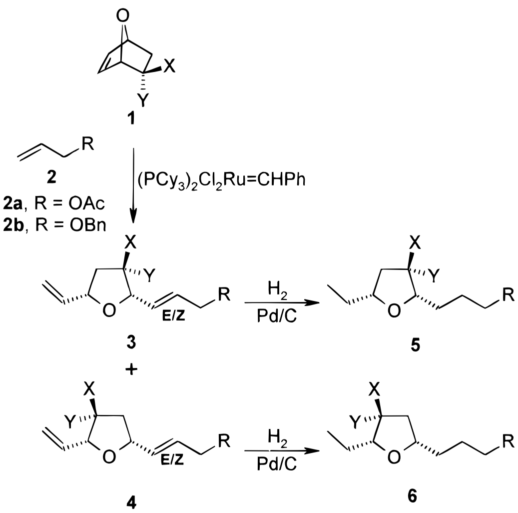
7-Oxanorbornenes (7-oxabicyclo[2.2.1]-5-heptenes), easily derived from the cycloaddition reaction of furans with substituted alkenes, can be considered as chirons equivalent to hexoses. The development of new methods of transformation of these compounds into a wide variety of both cyclic and open-chain targets with a high level of stereocontrol is an area of current interest.[1] On the other hand, olefin metathesis continues to emerge as a powerful approach for the construction of complex organic molecules.[2] Although the fundamentals of this reaction have already been established, not much investigation has been devoted to the regiochemical aspects of the process.[3]

Albeit 7-oxanorbornenes are known to undergo ring-opening metathesis generating a variety of functional polymers,[4] the intermolecular ring-opening metathesis of these compounds has been only scarcely considered to date.[5] We are particularly interested in the effect of the homoallylic substituents in the regiochemistry of the combination of ring-opening and selective cross-coupling metathesis, as a means of synthesizing the 2,3,5-trisubstituted tetrahydrofurans A or B (Scheme 1). As a matter of fact, it is known that the control of the regioselectivity by the remote substituent at C-2 of different types of reactions performed on the endocyclic C=C bond in 7-oxanorbornenes appears to differ depending on the reaction to be considered.[6−9]

Scheme 1



Scheme 2



1a, **3a**, **4a**, X, Y = C=O, R = OAc
1b, **3b**, **4b**, X = H, Y = OH, R = OAc
1c, **3c**, **4c**, X = H, Y = OAc, R = OAc
1d, **3d**, **4d**, X = H, Y = $OCOCH=CH_2$, R = OAc
1e, **3e**, **4e**, X, Y = OCH_2CH_2O, R = OAc
3f, **4f**, X, Y = OCH_2CH_2O, R = OBn
5a, **6a**, X, Y = C=O, R = OAc
5b, **6b**, X = H, Y = OH, R = OAc
5c, **6c**, X = H, Y = OAc, R = OAc
5d, **6d**, X = H, Y = $OCOCH_2CH_3$, R = OAc
5e, **6e**, X, Y = OCH_2CH_2O, R = OAc
5f, **6f**, X, Y = OCH_2CH_2O, R = OBn

Results and Discussion

2-Substituted 7-oxanorbornenes **1** were treated with alkenes **2** in the presence of Grubb's ruthenium catalyst[10] [$Cl_2(Cy_3P)_2Ru$=CHPh] to afford, after catalytic hydrogenation, the corresponding tetrahydrofuran derivatives **5** and **6** (Scheme 2).[11] The results of these experiments are given in Table 1. The inspection of these data puts forward that the reaction of ketone **1a** with alkene **2a** took place with no regioselectivity at all (entry 1). This was also the case with the alcohol **1b** (entry 2). On the other hand, the reaction of the acyloxy derivatives **1c,d** gave rise to the majority formation of the corresponding tetrahydrofurans **6c,d** (entries 3 and 4). It is worth

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(2) For selected recent reviews see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 371.

(3) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611. (b) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478−1479. For a recent account on the preferences of ring-closing metathesis on the synthesis of spirocyclic systems see: Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247.

(4) Review: Ivin, K. J. *Olefin Metathesis*; Academic Press: London, 1996. For recent references see: (a) Lynn, D. M.; Kanaoka, S.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 784. (b) Ball, C. P.; Barrett, A. G. M.; Poitont, L. F.; Smith, M. L.; Thorn, Z. E. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2453. (c) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627.

(5) To the best of our knowledge, only the ring-opening metathesis of 7-oxanorbornene derivatives with identical substitution at positions 2 and 3 has been previously reported: Schenider, M. F.; Lucas, N.; Velder, J. Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257

(6) For the regioselectivity in electrophilic additions see: (a) Vogel, P.; Fattori, D.; Gasparini, F.; le Drian, C. *Synlett* **1990**, 173. (b) Arjona, O.; de la Pradilla, R. F.; Pita-Romero, I.; Plumet, J.; Viso, A. *Tetrahedron* **1990**, *46*, 8199.

(7) For the regioslectivity in 1,3-dipolar cycloadditions see: (a) Arjona, O.; Domínguez, C.; de la Pradilla, R. F.; Mallo, A.; Manzano, C.; Plumet, J. *J. Org. Chem.*, **1989**, *54*, 5883. (b) Arjona, O.; de Dios, A.; de la Pradilla, R. F.; Mallo, A.; Plumet, J. *Tetrahedron* **1990**, *46*, 8179.

(8) For the regioselectivity in Diels−Alder reactions see: Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341.

(9) For the regioselectivity in the Pauson−Khand reaction see: Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 7338.

(10) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2179.

(11) Compounds **3** and **4** were obtained as mixtures of the corresponding *E* and *Z* alkenes.

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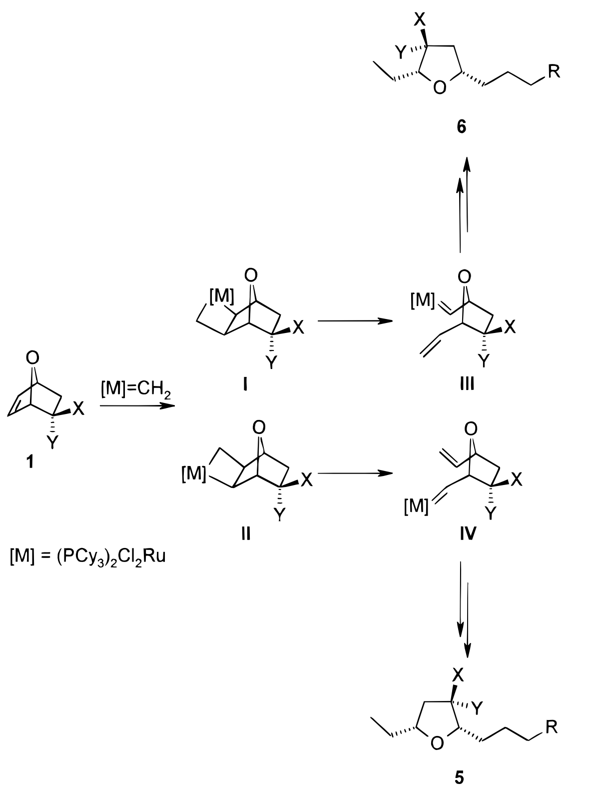
Table 1. Ring-Opening and Selective Cross-Coupling Metathesis of 7-Oxanorbornenes 1

no.	1	X, Y	2	R	5:6 (ratio,[a] %)[b]
1	**1a**	X, Y = C=O	**2a**	OAc	**5a:6a** (50:50, 75)
2	**1b**	X = H, Y = OH	**2a**	OAc	**5b:6b** (50:50, 80)
3	**1c**	X = H, Y = OAc	**2a**	OAc	**5c:6c** (19:81, 75)
4	**1d**	X = H, Y = OCOCH=CH_2	**2a**	OAc	**5d:6d** (23:77, 75)
5	**1e**	X, Y = OCH_2CH_2O	**2a**	OAc	**5f:6f** (20:80, 70)
6	**1e**	X, Y = OCH_2CH_2O	**2b**	OBn	**5f:6f** (20:80, 70)

[a] Determined by GC−MS. [b] Combined isolated yields after silica gel chromatography.

Scheme 3



mentioning that, in the case of **1d**, the combination of cross, ring-opening, and ring-closing metathesis was not observed.[12] Last, the reaction of the dioxolane **1e** took place with a good regioselectivity[13] in favor of the corresponding tetrahydrofuran **6** (entry 4), and this was also the case when alkene **2b** was used as the cross-coupling counterpart (entry 5).

To understand the orientation of the α-alkyl chains with respect to the β-substituent in the regioisomeric tetrahydrofurans **5** and **6**,[13] the postulated reaction course for the alkene metathesis reaction must be considered. Thus, according to the mechanism proposed by Chauvin,[14] the key step in the mechanism is the irreversible cycloaddition of the carbene species $(Cy_3P)_2Cl_2Ru{=}CH_2$ to the C=C bond of the bicyclic alkene **1** (Scheme 3). This insertion gives rise to a fused metallacyclobutane (intermediates **I** and **II**). This step is believed to be rate- and product-determining. The cycloreversion of the metallacyclobutane leads to ring opening, with formation a new carbene species (intermediates **III** and **IV**). Cycloaddition of the latter to the acyclic alkene **2** affords the observed products **5** or **6**. Therefore, the preferred orientation in the reaction should stem presumably from steric effects in the cycloaddition (intermediates **I** and **II**), although the electronic bias of the C=C bond in the starting materials **1**, as well as complexation effects, cannot be ruled out.

The results gathered in Table 1 revealed that the ring-opening methathesis of ketone **1a** took place with no regioselectivity. No effect of the polarization of the double bond by the carbonyl group on the regiochemical outcome of the reaction was observed,[7−9] and a similar stability of the corresponding intermediates (**Ia** or **IIa**) was put forward. In the case of alcohol **1b**, intermediate **IIb** should be unstabilized with respect to **Ib** as a result of steric interactions between the ligands on the metal and the OH group. However, no regioselectivity was observed in the ring-opening metathesis of alcohol **1b**. On the other hand, when the OH was protected in the form of the acyl derivative (**1c,d**), steric arguments favored the formation of intermediate **Ic,d**, leading to **6c,d**. This was also the case in the case of dioxolane **1e**, which gives tetrahydrofurans **6e** and **6f** as the major reaction products.

In conclusion, the study herein reported puts forward the control of the ring-opening metathesis reaction of 7-oxanorborn-5-enes by the remote substituent at C-2. This procedure constitutes a convenient method for the diastereoselective synthesis of trisubstituted tetrahydrofurans.[15]

Experimental Section

Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV and vanillin solution. Flash 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 200 or 300 MHz and 50.5 or 75.5 MHz, respectively. 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.

Ring-Opening and Cross-Coupling Metathesis of Compounds 1 with Alkenes 2. General Procedure. To a solution of **1** (0.46 mmol) and alkene **2** (0.46 mmol) in anhydrous CH_2Cl_2 (20 mL) was added $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.023 mmol) dissolved in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 2 h for compounds **1a** and**1c**−**e** and 24 h for compound **1b**. 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 product was dissolved in MeOH (5 mL), 10% Pd on charcoal (7 mg) was added, and the mixture was hydrogenated at 50 PSI for 3 h. Filtration of the catalyst and evaporation of the solvent afforded a brown oil that was purified by chromatography (silica gel, hexane/ethyl acetate 3:2).

(2*S,5*R**)-2-(3′-Acetoxypropyl)-5-ethyl-3-oxotetrahydrofuran (5a) and (2*R**,5*S**)-5-(3′-Acetoxypropyl)-2-ethyl-3-oxotetrahydrofuran (6a).** **5a**:**6a** = 50:50; colorless oil; IR ($CHCl_3$) ν 1740, 1715; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7 Hz, 3H, **5a**), 1.0 (t, J = 7.5 Hz, 3H, **6a**), 1.60−1.90 (m, 7H), 2.05 (s, 3H), 2.50 (dd, J = 17 Hz, J = 5.5 Hz, 1H), 3.75 (m, 1H), 4.10 (m, 3H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 202.4, 171.8, 82.5 (**6a**), 80.9 (**5a**), 78.2 (**5a**), 75.3 (**6a**), 64.1, 43.8 (**6a**), 42.4 (**5a**), 32.1 (**6a**), 28.2 (**5a**), 27.1 (**5a**), 25.0 (**6a**), 24.2 (**6a**), 20.5, 9.5. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.46. Found: C,61.72; H, 8.62.

(2*S,3*S**,5*R**)-2-(3′-Acetoxypropyl)-5-ethyl-3-hydroxytetrahydrofuran (5b) and (2*R**,3*R**,5*S**)-5-(3′-Acetoxypropyl)-**

(12) The combination of cross, ring-opening, and ring-closing metathesis has been reported in the case of *endo*-2-substituted norborn-5-enes. See: Stragies, R.; Blechert, S. *Synlett* **1998**, 169.

(13) Compounds **5** and **6** were separated by GC or HPLC. The structural assignment of both regioisomers was based on the analysis of their MS fragmentation pattern. See the Supporting Information.

(14) Hérisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.

(15) Harmange, J.-C.; Figadère, B. *Tetrahedron Asymmetry* **1993**, *4*, 1711−1754.

2-ethyl-3-hydroxytetrahydrofuran (6b). 5b:**6b** = 50:50; colorless oil; IR ($CHCl_3$) ν 3250, 1730; ^{1}H NMR (200 MHz, MeOH-d_4) δ 0.95 (t, J = 7 Hz, 3H, **5b**), 0.98 (t, J = 7 Hz, 3H, **6b**), 1.46−1.78 (m, 7H), 2.01 (s, 3H), 2.30−2.45 (m, 1H), 3.40−3.80 (m, 2H), 4.11 (m, 2H), 4.20 (m, 1H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 173.8, 88.7 (**6b**), 86.5 (**5b**), 83.0 (**5b**), 81.0 (**6b**), 75.7 (**5b**), 75.3 (**6b**), 68.2, 44.8 (**6b**), 44.4 (**5b**), 36.2 (**6b**), 32.6 (**5b**), 29.2 (**5b**), 29.1 (**5b**), 25.5 (**6b**), 23.3 (**6b**), 13.5 (**6b**), 13.3 (**5b**). Anal. Calcd for $C_{11}H_{29}O_4$: C, 61.37; H, 8.89. Found: C, 61.52; H, 9.01.

(2*S,3*S**,5*R**)-3-Acetoxy-2-(3′-acetoxypropyl)-5-ethyltetrahydrofuran (5c) and (2*R**,3*R**,5*S**)-3-Acetoxy-5-(3′-acetoxypropyl)-2-ethyltetrahydrofuran (6c). 5c**:**6c** = 19:81; colorless oil; IR ($CHCl_3$) ν 1740, 1280, 1210; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7 Hz, 3H, **5c**), 0.93 (t, J = 7 Hz, 3H, **6c**), 1.45−1.80 (m, 7H), 2.02 (s, 3H), 2.05 (s, 3H), 2.35−2.55 (m, 1H), 3.50−3.90 (m, 2H), 4.10 (m, 2H), 5.25 (m, 1H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 171.2, 170.6, 83.1 (**6c**), 80.9 (**5c**), 78.7 (**5c**), 75.0, 74.6 (**6c**), 64.3, 39.3 (**6c**), 38.9 (**5c**), 32.3, 25.4, 22.1, 21.0, 20.9, 10.6 (**6c**), 10.5 (**5c**); MS m/z (%) (**5c**) 138 (16), 112 (15), 109 (24), 97 (12), 71 (46), 43 (100); MS m/z (%) (**6c**) 138 (6), 112 (7), 109 (15), 97 (59), 71 (15), 43 (100). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58. Found: C,60.62; H, 8.61.

(2*S,3*S**,5*R**)-2-(3′-Acetoxypropyl)-5-ethyl-3-tetrahydrofuranyl Propanoate (5d) and (2*R**,3*R**,5*S**)-5-(3′-Acetoxypropyl)-2-ethyl-3-tetrahydrofuranyl Propanoate (6d). 5d**:**6d** = 23:77; colorless oil; IR ($CHCl_3$) ν 1735, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H, **5d**), 0.92 (t, J = 7 Hz, 3H, **6d**), 1.10 (t, J = 7.5 Hz, 3H), 145−180 (m, 7H), 2.00 (s, 3H), 230 (q, J = 7.5 Hz, 2H), 2.35−2.50 (m, 1H), 3.50−3.80 (m, 2H), 4.05 (m, 2H), 5.20 (m, 1H); ^{13}C NMR (50.5 MHz, $CDCl_3$) ? 174.0, 171.1, 83.2 (**6d**), 80.9 (**5d**), 79.1 (**5d**), 74.7, 74.4 (**6d**), 64.4, 39.3 (**6d**), 38.9 (**5d**), 32.4, 27.8, 25.6 (**5d**), 25.3 (**6d**), 22.1, 20.9, 10.6 (**6d**), 10.2 (**5d**), 9.2. MS m/z (%) (**5d**) = 171 (7), 138 (21), 112 (19), 109 (26), 97 (10), 71 (34), 57 (100), 43 (39); MS m/z (%) (**6d**) 171 (2), 138 (7), 112 (2), 109 (16), 97 (65), 71 (9), 57 (100), 43 (43). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.75; H, 8.88. Found: C, 61.85; H, 8.92.

(2*S,5*R**)-2-(3′-Acetoxypropyl)-5-ethyl-3,3-ethylendioxytetrahydrofuran (5e) and (2*R**,5*S**)-5-(3′-Acetoxypropyl)-2-ethyl-3,3-ethylendioxytetrahydrofuran (6e). 5e**:**6e** = 21:79; colorless oil; IR ($CHCl_3$) ν 1740, 1250, 1230; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H, **5e**), 0.98 (t, J = 7.5 Hz, 3H, **6e**), 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, **6e**), 3.62 (dd, J = 7.6, 5.1 Hz, 1H, **5e**), 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 (**6e**), 82.4 (**5e**), 78.1 (**5e**), 76.0 (**6e**), 65.1, 64.4, 64.1, 43.3 (**6e**), 42.9 (**5e**), 31.8 (**6e**), 28.3 (**5e**), 26.7 (**5e**), 25.3 (**5e**), 25.0 (**6e**), 23.2 (**6e**), 20.9, 10.5; MS m/z (%) (**5e**) 258 (11), 229 (14), 128 (18), 113 (22), 99 (100), 55 (22), 43 (34); MS m/z (%) (**6e**) 258 (2), 157 (36), 141 (16), 113 (53), 99 (100), 55 (22), 43 (45). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58. Found: C, 60.63; H, 8.70.

(2*S,5*R**)-2-(3′-Benzyloxypropyl)-5-ethyl-3,3-ethylenedioxytetrahydrofuran (5f) and (2*R**,5*S**)-5-(3′-Benzyloxypropyl)-2-ethyl-3,3-ethylenedioxytetrahydrofuran (6f). 5c**:**6c** = 20:80; colorless oil; IR ($CHCl_3$) ν 1735, 1290, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H, **5f**), 0.95 (t, J = 7 Hz, 3H, **6f**), 1.40−1.80 (m, 7H), 2.10 (dd, J = 13 Hz, J = 6 Hz, 1H), 3.50−3.65 (m, 2H), 3.80−4.06 (m, 4H), 4.50 (s, 2H, **6f**), 4.52 (s, 2H, **5f**), 7.30 (m, 5H). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.65; H, 8.76.

Supporting Information Available: NMR and MS spectra of compounds **5c**−**e** and **6c**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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