Pergamon

Tetrahedron Letters 42 (2001) 239–242

TETRAHEDRON LETTERS

Formation of dissymmetric eight-membered silalketals by ring-closing metathesis and their conversion to spiroketals

Jean-Guy Boiteau, Pierre Van de Weghe and Jacques Eustache*

Laboratoire de Synthèse Organique et Chimie Microbienne associé au CNRS. Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse, 3, Rue Alfred Werner, F-68093 Mulhouse Cedex, France

Received 30 August 2000; accepted 30 October 2000

Abstract—Eight-membered unsymmetrical silalketals are formed by RCM of mixed allyl/homoallyl silalketals. They are crucial intermediates in a short synthetic sequence to spiroketals illustrated in this paper by the synthesis of the C_{28}–C_{38} portion of okadaic acid.

Recent reports indicate that synthetic molecules containing the spiro [5.5] ketal system (commonly found in a number of naturally occurring substances), may exhibit interesting pharmacological activities.[1,2] To fully assess the potential of these molecules, the synthesis of series of analogs and the development of structure–activity relationships will be required. The most widely used strategy for spiroketal preparation involves an acid-catalyzed cyclization of dihydroxyketones (spiroketalization) as a key step. Although the spiroketalization itself is a very facile process, access to the dihydroxyketone precursor is not always easy, in particular for complex molecules.[3] We wanted to develop an alternative strategy in which two fully functionalized fragments would be first assembled, the resulting adducts being converted to dihydroxyketones then to the corresponding spiroketals in a few simple steps. Obviously, for such an approach to be successful, the reaction conditions for the coupling and subsequent steps must be compatible with most functional groups. For some time, we have been interested in applications of the ring-closing metathesis (RCM) reaction in total synthesis. The main advantages of RCM are its wide applicability and its remarkable tolerance to functional groups. The use of temporary tethers in conjunction with RCM renders the method even more versatile and may be used for the stereoselective coupling of olefins. This led us to envisage the approach shown in Fig. 1, in which the key step is the RCM of a mixed allyl/homoallyl silalketal. The preparation of (mostly) symmetrical seven-membered[4–7] and a few 10- or 11-membered[6] cyclic silalketals by RCM and their conversion to diols has been described but, to the best of our knowledge, the method has not yet been applied to eight-membered silalketals despite the potential usefulness of these intermediates. For example the presence of an exclusively *cis* double bond and of two differentiated (allylic/homoallylic) hydroxyl groups should allow a range of selective transformations. In this communication, we describe the preparation of dissymmetric eight-membered silalketals by RCM and show that they can readily be converted to spiroketals.[8] To illustrate our strategy we have chosen to prepare by this method the known C_{28}–C_{38} spiroketal moiety of okadaic acid (**8**: Scheme 1).[9]

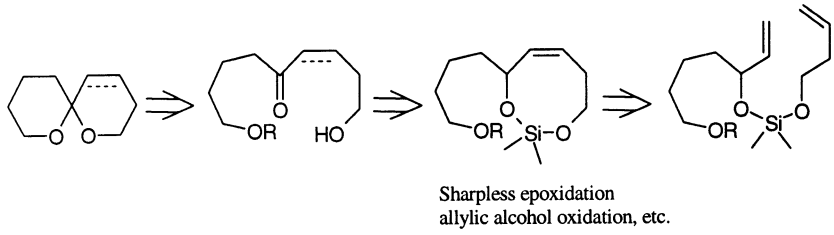
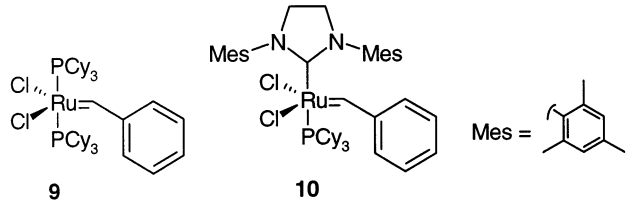


Figure 1.

* Corresponding author. Fax: 33 (0)3 89 336860; e-mail: j.eustache@univ-mulhouse.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(00)01929-8

The starting compounds (**1** and **3**) were readily obtained following literature procedures. Thus, the chiral homoallylic alcohol **1** was prepared by diastereoselective addition of crotyl tributyl stannane,[10,11] to (*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropanal,[12] and the racemic monosilylated ene-diol **3** was prepared as described previously.[13] The two precursors **1** and **3** were linked through a dimethylsilyl bridge as indicated in Scheme 1, to provide the bis-alkoxysilane **4** as a 1:1 mixture of diastereoisomers. This mixture was submitted to two sets of RCM conditions, using 'Grubbs' catalysts' **9** and **10**.

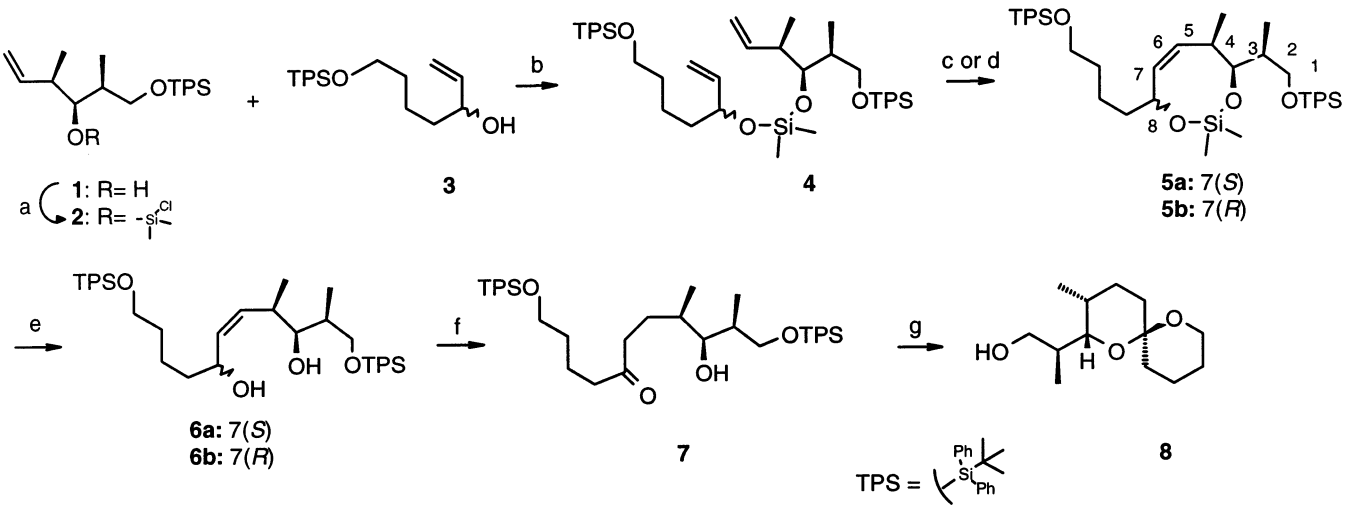


The outcome of the RCM reaction using catalyst **9** was interesting as only a single cyclized product (**5a**) was formed (as evidenced by NMR) while recovered unreacted **4** was strongly enriched in one isomer. We tentatively attribute the *S* configuration at the allylic center (C_7) in **5a** on the basis of nOe data: a strong (20%) positive nOe effect between H_4 and H_7 clearly indicated that both protons were axially oriented (Fig. 2), pointing towards structure **5a**.

To further confirm that diastereoselective differentiation had indeed taken place, the silyl bridge in unreacted **4** was cleaved and the optical rotation of recovered **3** was measured; the positive value observed implies that the RCM reaction occurred stereoselectively.[14]

In contrast, using the recently described complex **10**,[15] we were pleased to observe a smooth and complete RCM leading to a 1:1 mixture of diastereoisomers **5a** and **5b** which was directly converted by brief acidic treatment to the corresponding mixture of diols **6** (65% over two steps).[16] **6a** and **6b** could be easily separated by chromatography but, from a synthetic viewpoint, it is more convenient to use the mixture **6**.

Until now, attempts to directly effect the conversion **6**→**7** using a variety of transition metal-induced allylic alcohol/ketone isomerization failed. We then turned to the short sequence shown in Scheme 1 in which the crude ketone **7** (a mixture of ketone and hemiketal) was obtained by sequential selective oxidation of the allylic



Scheme 1. Reagents and conditions: (a) BuLi, Me_2SiCl_2, THF, −78°C, 10 min; (b) **3**, imidazole, THF, 20°C, 16 h, 92% (for steps (a) and (b)); (c) **9** (0.25 equiv.), benzene, reflux, 48 h, 46%; (d) **10** (0.1 equiv.), benzene, reflux, 48 h; (e) CF_3COOH (0.2 equiv.), THF/MeOH, 20°C, 3 h, 65% (for steps (d) and (e)); (f) (i) MnO_2 (70 equiv.), CH_2Cl_2/ethyl acetate, 20°C, 24 h, (ii) H_2, Pd/C; (g) (i) NBu_4F, THF, (ii) CF_3COOH, toluene, 20°C, 60% (for steps (f) and (g)).

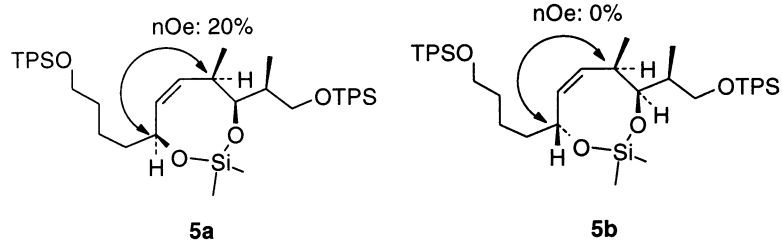


Figure 2. nOe effects in **5a** and **5b**.

hydroxyl group in **6** using MnO_2, followed by catalytic hydrogenation. Removal of the silyl protecting groups with tetrabutylammonium fluoride and classical trifluoroacetic acid-induced spiroketalization gave **8** as a single isomer, in agreement with earlier findings.[9,17] The conversion **6**→**8** was effected in 60% overall yield, without purification of intermediates.

In conclusion, we have described a short and simple RCM-based sequence for the preparation of spiro[5.5] ketals. The mild reaction conditions used and the facile preparation of the precursors suggest that this new approach should be widely applicable. This work and additional functionalization possibilities of the eight-membered silalketals intermediates are under study in our laboratory.

Acknowledgements

We thank Drs. Didier Le Nouen and Stéphane Bourg for help with NMR recording and interpretation.

References

1. Mitsuhashi, S.; Shima, H.; Kawamura, T.; Kikuchi, K.; Oikawa, M.; Ichihara, A.; Oikawa, H. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 2007–2012.
2. Uckun, F. M.; Mao, C.; Vassilev, A. O.; Huang, H; Jan, S.-T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541–545.
3. For a review on the chemistry of spiroketals, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661. The dihydroxyketone precursor is almost always obtained by addition of an organometallic reagent onto various nucleophiles (ketone, lactone, …) which implies severe restrictions with regard to functional groups present in the fragments to be coupled.
4. Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768–6769. The conversion of a seven-membered silylketal into altritol is described in this paper.
5. Hoye, T. H.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429–1432.
6. Lobbel, M.; Köll, P. *Tetrahedron*: *Asymmetry* **2000**, *11*, 393–396.
7. Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517–1519.
8. To the best of our knowledge, RCM has been used in two instances for the preparation of spiroketals. Conceptually, however, the approaches are entirely different: (a) Van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. *Tetrahedron Lett.* **1998**, *39*, 6061–6064. (b) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247–3250
9. Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523–2533. Spiroketals are often constituted of thermodynamic mixtures of isomers. The C_{28}–C_{38} spiroketal moiety of okadaic acid has been reported to exist as a single isomer.
10. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883–1886.
11. Marshall, J. A.; Pavlovich, M. R. *J. Org. Chem.* **1998**, *63*, 4381–4384.
12. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348.
13. Lopez-Tucanda, P. L.; Jones, K.; Brownbridge, P. *Tetrahedron Lett.* **1991**, *32*, 2261–2264.
14. The monoprotected diol **3** has been described only in the racemic form, the $[\alpha]_D$ value of recovered **3** in our experiment cannot be used to support our structural assignment for **5**. However, the positive optical rotation indicates that diastereoselectivity had occurred.
15. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
16. For analytical purposes, the two isomers **5a** and **5b** were separated by chromatography and the nOe effects between H_4 and H_7 determined: whereas a strong (+20%) nOe effect was observed for **5a**, no significant signal enhancement was seen for **5b**.
17. Experimental details:
RCM of diene ***5***: To a solution of diene **5** (175 mg, 0.22 mmol) in benzene (3 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine] ruthenium(IV) dichloride (**10**, 10 mg, 11 μmol, 5 mol%). The resulting mixture was refluxed for 48 h. The solvents were removed in vacuo and the residue was filtered over a short pad of silica gel (5% ethyl acetate in cyclohexane) to removed the metallic residues. The oil thus obtained was dissolved in THF/MeOH (2/1), trifluoroacetic acid (5 μL, 20 mol%) was added, and the solution was stirred for 3 h at room temperature. Flash chromatography over silica gel (15% ethyl acetate in cyclohexane) provided the desired diols **6a** (48 mg) and **6b** (52 mg). Overall yield: 65% over two steps.
6a: $[\alpha]_D^{20} = -7.7$ (*c* 1.3, $CHCl_3$); anal. calcd: C, 74.8; H, 8.6; found: C, 74.65; H, 8.6.
^{1}H NMR ($CDCl_3$, 250 MHz): 7.69–7.66 (m, 8H, Ar*H*); 7.48–7.34 (m, 12H, Ar*H*); 5.37 (dd, $J = 8.9$, 10.9, 1H, CH=C*H*CHCH$_2$); 5.23 (t, $J = 10.8$, 1H, C*H*=CHCH-CH$_2$); 4.39 (m, 1H, MeCHC*H*OH); 3.81–3.62 (m, 5H, TPSOCH_2, TPSOCH_2 and HOC*H*CHMe); 3.01 (broad s, 1H, O*H*); 2.70 (m, 1H, MeC*H*CH=CH); 1.81 (m, 2H, SiOCH$_2$C*H*Me and O*H*); 1.63–1.33 (m, 6H, (CH$_2$)$_3$); 1.07 (2s, 18H, *t*BuSi); 1.07 (d, 3H, CH_3); 0.97 (d, $J = 7$, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 62.9 MHz): 135.7, 135.6, 134.4, 132.7, 129.9, 129.5, 127.8, 127.6, 77.8, 69.8, 67.7, 63.8, 37.3, 36.5, 36.4, 32.5, 26.9, 21.8, 19.2, 18.2, 9.8.
6b $[\alpha]_D^{20} = -1.2$ (*c* 0.8, $CHCl_3$); anal. calcd: C, 74.8; H, 8.6; found: C, 74.03; H, 8.58.
^{1}H NMR ($CDCl_3$, 250 MHz): 7.67–7.64 (m, 8H, Ar*H*); 7.47–7.33 (m, 12H, Ar*H*); 5.35 (t, $J = 9.9$, 1H, CH=C*H*CH-CH$_2$); 5.22 (t, $J = 10.6$, 1H, C*H*=CHCH-CH$_2$); 4.40 (m, 1H, MeCHC*H*OH); 3.77–3.59 (m, 5H, TPSOCH_2, TPSOCH_2 and HOC*H*CHMe); 2.85 (broad s, 1H, O*H*); 2.67 (m, 1H, MeC*H*CH=CH); 1.70–1.32 (m, 8H, (CH$_2$)$_3$, SiOCH$_2$C*H*Me and O*H*)); 1.13 (d, $J = 6.5$, 3H, CH_3); 1.07 and 1.03 (2s, 18H, *t*BuSi); 0.88 (d, $J = 7$, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 62.9 MHz): 135.7, 135.6, 134.9, 132.3, 129.9, 129.5, 127.8, 127.6, 77.8, 69.5, 67.9, 63.7, 37.3, 36.8, 36.3, 32.6, 26.9, 21.7, 19.2, 18.6, 9.4.

Conversion ***6→8***: To a solution of a 1:1 mixture of diols **6a** and **6b** (60 mg, 83 μmol) in dichloromethane/ethyl acetate 8/2 (2 mL) was added activated manganese dioxide (390 mg, 4.5 mmol). The resulting suspension was stirred for 12 h with occasional sonication whereupon more manganese dioxide was added (150 mg, 1.7 mmol) and the suspension was stirred for an additional 12 h (NMR control showed 75% conversion). The suspension was filtered and concentrated in vacuo and the resulting oil directly dissolved in methanol/THF 9:1 and hydrogenated for 4 h using Pd/C (10 mol%); after removal of the catalyst and solvents, the residue was dissolved in THF (5 mL) and a solution of tetrabutylammonium fluoride (1 M in THF, 180 μL, 0.18 mmol) was added. The reaction mixture was stirred overnight, the solvents were removed in vacuo and the residue was azeotropically dried (10 mL toluene) in presence of trifluoroacetic acid (20 μL, 0.26 mmol). The solvents were evaporated and the residue was chromatographed over silica gel (50% ethyl acetate in cyclohexane) to provide the desired spiroketal **8** (11 mg, 48 μmol) in 60% yield. **8**: $[\alpha]_D^{20} = +67$ (*c* 0.75, $CHCl_3$). Reported: $[\alpha]_D^{20} = +69$ (*c* 1.55, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): 3.68 (m, 1H); 3.65 (dd, $J = 4$, 10.4, 1H); 3.57 (m, 1H); 3.56 (dd, $J = 2$, 10, 1H); 3.48 (dd, $J = 6.4$, 10.8, 1H); 2.05 (dddd, $J = 4.6$, 4.6, 13.8, 13.8, 1H); 1.90–1.75 (m, 3H); 1.69–1.34 (m, 8H), 1.13 (d, $J = 6.8$, 3H); 0.95 (d, $J = 7$, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 72.6, 64.8, 60.4, 37.5, 35.8, 30.3, 28.0, 26.5, 25.4, 18.7, 14.4, 11.4. Reported: ($CDCl_3$, 125 MHz): 95.7, 72.6, 64.9, 60.4, 37.6, 35.9, 30.3, 28.1, 26.4, 25.4, 18.7, 14.4, 11.4.