The First Synthesis of a 10-Membered Ring by Olefin Metathesis: Jasmine Ketolactone

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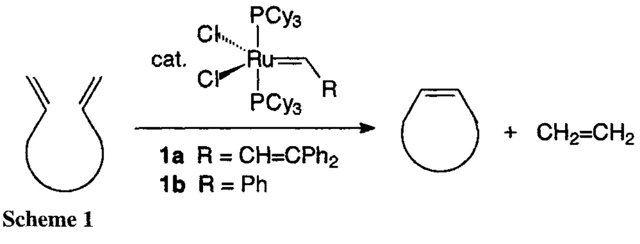
Received 14 April 1997

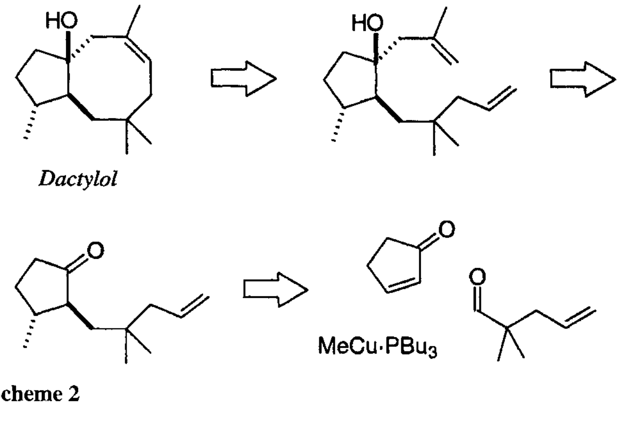
Abstract: An unprecedentedly short route to jasmine ketolactone (*Z*)-**2** and its *E*-isomer is described, which is based on the efficient formation of the 10-membered ring via ring closing olefin metathesis (RCM) of diene **8**. The latter is conveniently prepared by a three component coupling reaction consisting of the 1,4-addition of the lithium enolate of 3-butenyl (diphenylmethylsilyl)acetate **6** to 2-cyclopentenone and subsequent trapping of the enolate thus formed with allyl iodide.

Olefin metathesis is presently evolving into a mature tool for organic synthesis due to the development of a new generation of alkylidene complexes which convert *in situ* into highly performant and exceedingly tolerant catalysts.[1,2] Most notable among them are the ruthenium carbenes **1a**,**b** developed by *Grubbs et al.* due to the ease of preparation, their high stability and the excellent compatibility with a wide range of polar functional groups.[3] These and related pre-catalysts have been applied with considerable success to the ring-opening metathetic polymerization (ROMP) of cycloalkenes as well as to the reverse process, *i. e.* the ring closing metathesis (RCM, Scheme 1) of dienes. It is well established that ROMP proceeds particularly well when medium sized cycloalkenes are used as the substrates since the release of the ring strain provides a formidable driving force for the forward reaction.[1] Conversely, this feature makes clear that the formation of cycloalkenes of 8-11 ring atoms by RCM constitutes a particular challenge.



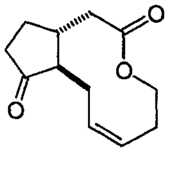
Scheme 1

However, a few model studies seem to indicate that medium sized rings can be obtained by RCM, provided that the entropy gained by bisecting the diene precursor, with evaporative loss of the ethene formed as the cut-off by-product, compensates for the unfavorable increase in enthalpy during cyclization.[4] We have recently illustrated this aspect by a straightforward approach to the marine metabolite dactylol, which relied on an expeditious assembly of the carbon skeleton of the target by a three-component coupling process followed by the highly efficient cyclization of the cyclooctenoid system via RCM (Scheme 2).[5]



Scheme 2

Encouraged by this result and related ones in the macrocyclic series[6] we explored whether RCM may lend itself to the formation of 10-membered rings which are among the most difficult to cyclize.[7] To the best of our knowledge, no successful application of RCM to such compounds has been reported so far.



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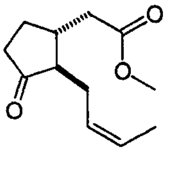

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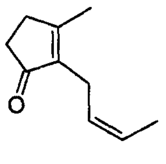

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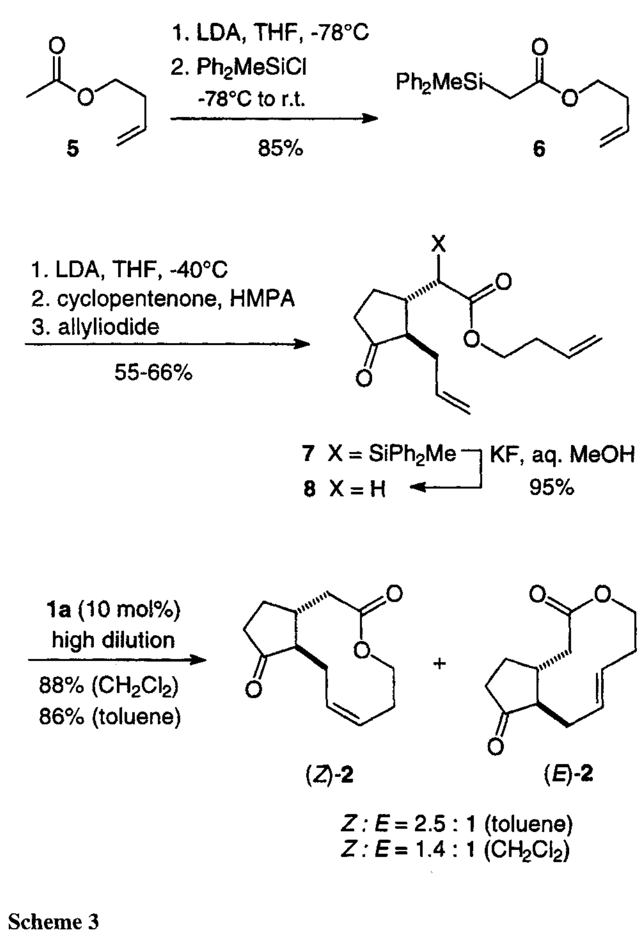
Among the wealth of naturally occurring decanolides[8] we have chosen jasmine ketolactone **2** as our target. This minor component of the essential oil of jasmine (*Jasminum grandiflorum* L.) is biosynthetically related to the more abundant odorants methyl jasmonate **3** and jasmone **4**.[9,10] All known approaches to **2** involve a macrolactonization as the key step and are rather lengthy and low yielding.[11] We now disclose a significantly shorter route to its *trans*-fused [8.3.0] bicyclic framework based on a three component coupling/RCM strategy as outlined in Scheme 3.



Scheme 3

A standard acetylation of 3-butenol (Ac_2O, pyridine, DMAP) provides ester **5** in 92% yield which is efficiently C-silylated to afford **6** (LDA, $Ph_2MeSiCl$, THF, 85%) by closely following a literature procedure.[12,14] It is well established that lithium enolates of α-heteroatom substituted esters are weaker bases and softer nucleophiles than their unsubstituted analogues, thus favoring kinetic 1,4- over 1,2-addition to an enone.[13] In fact, reaction of 2-cyclopentenone with the lithium enolate of **6** in a THF/HMPA mixture, followed by addition of an excess of allyl iodide in order to trap the kinetically defined enolate formed in the Michael addition step affords the *trans*-disubstituted cyclopentanone derivative **7** in reasonable to good yield.[13] Subsequent proto-desilylation by means of KF in $MeOH/H_2O$ (4/1) is almost quantitative, providing diene **8** as a suitable cyclization precursor. RCM is then effected by slowly combining solutions of **8** and the ruthenium carbene **1a** (10 mol%), in CH_2Cl_2 each, via two dropping funnels over a period of ~ 12h and refluxing of the resulting mixture until TLC shows complete conversion of the substrate (24-48h). This effects the amazingly clean formation of the desired 10-membered ring compound **2**, which was isolated in 88% yield as a mixture of the geometrical isomers. Jasmine ketolactone (*Z*)-**2** thus formed as the slightly preponderant isomer can be separated from its (*E*)-analogue by preparative HPLC. Changing the solvent from CH_2Cl_2 to toluene, allowing the reaction to be performed at 70°C, hardly affected the yield and improved the *Z*:*E* ratio only slightly.[15] This result is very much in line with our previous observations in the macrocyclic series.[6c] Thus, jasmine ketolactone together with its previously unknown (*E*)-isomer are obtained in only 5 steps in a combined yield of 35-43% starting from commercially available substrates.

This synthesis highlights some fundamental aspects of RCM: being the first example of a successful preparation of a 10-membered ring by this method, it nicely illustrates the utility and exceptionally wide scope of this transformation. However, it also demonstrates that we are presently unable to predict - and even more so - to control the stereochemistry of the newly formed double bond of a cycloalkene possessing $\geq$ 10 ring atoms.[6] Further improvements of the methodology in this respect are highly desirable. Finally, this synthesis together with our recent approach to dactylol[5] demostrate that a well orchestrated combination of a three component assembly followed by RCM consitutes a highly flexible, modular and performant strategy for the construction of complex target molecules. Further investigations along these lines are being actively pursued in our laboratory.

Acknowledgement. We would like to thank the Fonds der Chemischen Industrie, Frankfurt, for generous financial support.

References and Notes

(1) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, New York, **1997**.

(2) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.

(3) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858-9859. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179-2181.

(4) (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109. (b) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856. (c) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251-7264. (d) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169-1170. (e) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291-4298. (f) Winkler, J. D.; Stelmach, J. E.; Axten, J. *Tetrahedron Lett.* **1996**, *37*, 4317-4318. (g) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478-1479. (h) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *J. Chem. Soc. Chem. Commun.* **1996**, 2231-2232. (i) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127-130.

(5) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746-8749.

(6) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942-3943. (b) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005-7008. (c) Fürstner, A.; Langemann, K. *Synthesis*, **1997**, 792.

(7) Reviews on medium sized rings: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777-2849. (c) For a discussion of cyclizations as a function of the ring size see i. a.: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95-102.

(8) Review: Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365-375.

(9) (a) Demole, E.; Willhalm, B.; Stoll, M. *Helv. Chim. Acta* **1964**, *47*, 1152-1159. (b) Naves, Y. R.; Grampoloff, A. V. *Helv. Chim. Acta* **1942**, *25*, 1500-1514.

(10) For applications of olefin metathesis to the preparation of structurally related cyclopentanone derivatives see: (a) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003-13014. (b) Hölder, S.; Blechert, S. *Synlett* **1996**, 505-506.

(11) (a) Gerlach, H.; Künzler, P. *Helv. Chim. Acta* **1978**, *61*, 2503-2509. (b) Kitahara, T.; Iwamoto, M.; Takagi, Y.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1984**, *48*, 1731-1734. (c) Shimizu, I.; Nakagawa, H. *Tetrahedron Lett.* **1992**, *33*, 4957-4958. (d) Nishi, T.; Kitahara, T. *Proc. Japan Acad.* **1995**, *71B*, 20-23.

(12) Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418-2419.

(13) Oppolzer, W.; Guo, M.; Baettig, K. *Helv. Chim. Acta* **1983**, *66*, 2140-2144.

(14) Selected spectroscopic data of new compounds:
5: IR: 3081, 2982, 2960, 2906, 1743, 1643, 1457, 1435, 1385, 1365, 1242, 1040, 995, 920 cm^{-1}.- ^1H NMR (200 MHz, $CDCl_3$): δ 5.79 (ddt, 1H), 5.17-5.04 (m, 2H), 4.12 (t, 2H), 2.38 (tq, 2H), 2.04 (s, 3H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 134.1, 117.2, 63.5, 33.1, 20.9.- MS (70 eV): *m/z* (rel. intensity): 115 (<1, [M^+]), 73 (16), 54 (45), 43 (100), 39 (14).
6: IR: 3071, 3050, 3012, 2958, 1722, 1642, 1428, 1406, 1247, 1142, 1115, 1095, 918, 811, 733, 699 cm^{-1}.- ^1H NMR (200 MHz, $CDCl_3$): δ 7.57-7.37 (m, 10H), 5.62 (ddt, 1H), 5.05-4.95 (m, 2H), 3.94 (t, 2H), 2.42 (s, 2H), 2.16 (tq, 2H), 0.69 (s, 3H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.2, 135.1, 134.5, 134.2, 129.7, 128.0, 116.9, 63.4, 33.0, 25.0, -3.8.- MS (70 eV): *m/z* (rel. intensity): 310 (9, [M^+]), 295 (26), 253 (15), 239 (17), 233 (100), 197 (96), 191 (33), 181 (10), 179 (13), 163 (12), 137 (36), 105 (13), 55 (15).
7 ($\approx$1.4:1 mixture of isomers): IR: 3071, 2960, 2905, 1740, 1713, 1641, 1429, 1310, 1263, 1158, 1119, 998, 918, 792, 736, 700 cm^{-1}.- ^1H NMR (200 MHz, $CDCl_3$, characteristic data): δ 7.60-7.32 (m, 10H), 5.77-5.44 (m, 2H), 5.06-4.92 (m, 4H), 0.82 (s, 1.4H), 0.77 (s, 1H).- ^{13}C NMR (50 MHz, $CDCl_3$, characteristic data) [minor isomer]: δ [219.9], 219.5, [175.2], 174.4, -2.9, [-3.8].- MS (70 eV): *m/z* (rel. intensity): 432 (4, [M^+]), 310 (14), 295 (18), 197 (100), 191 (11), 137 (16), 55 (21).
8: IR: 3078, 2960, 2931, 2909, 1737, 1641, 1460, 1437, 1410, 1390, 1335, 1265, 1232, 1171, 994, 918 cm^{-1}.- ^1H NMR (200 MHz, $CDCl_3$): δ 5.84-5.62 (m, 2H), 5.16-5.01 (m, 4H), 4.16 (t, 2H), 2.83-1.42 (m, 12H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ 218.6,

172.0, 135.0, 133.9, 117.4, 117.3, 63.6, 53.7, 38.8, 37.8, 37.7, 33.1, 32.2, 27.1.- MS (70 eV): *m/z* (rel. intensity): 236 (42, $[M^+]$), 165 (18), 136 (10), 123 (100), 93 (15)81 (10), 79 (20), 67 (14), 55 (75).

(15) Preparation of **2** by RCM: A flame dried 250 mL three-necked flask equipped with a magnetic stirring bar, a reflux condenser connected to the argon line and two pressure equilizing dropping funnels is charged with toluene (50 mL). Solutions of the diene **8** (200 mg, 0.85 mmol) and the ruthenium carbene **1a** (80 mg, 0.085 mmol) in toluene (50 mL) each are simultaneously added from the dropping funnels to the warm toluene (70°C) over a period of ≈ 12h. Stirring is continued at that temperature until TLC shows complete conversion of the substrate (≈ 48h). For work-up the solvent is evaporated and the crude product is purified by flash chromatography (Merck silica gel 60, 230-400 mesh) using hexane/ethyl acetate (4/1) as the eluent. This affords a mixture of (*Z*)-**2** and (*E*)-**2** as a pale yellow oil (152 mg, 86%, *Z*:*E* = 2.5:1), which can be separated by preparative HPLC (MD LC1; 250 mm Zorbax-SIL, ∅ 4.5 mm; mobile phase: *n*-heptane : 2-propanol = 95 : 5, 4.9 MPa, 1 ml/min, 308 K). Selected data:

(*Z*)-**2**: IR: 3007, 2966, 2921, 2855, 1738, 1724, 1456, 1403, 1288, 1240, 1140, 1115, 1096, 1029, 1017, 987, 811, 735, 661. - ^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (m, 2H), 4.64 (td, 1H, *J* = 4.7, 10.6), 3.79 (dt, 1H, *J* = 3.8, 10.3), 2.76 (dd, 1H, *J* = 2.8, 14), 2.60-2.75 (br. m, 1H), 2.42-2.53 (m, 4H), 2.04-2.19 (m, 4H), 1.91 (td, 1H, *J* = 3.8, 12.2), 1.41-1.54 (m, 1H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.2, 172.0, 131.2, 126.0, 62.2, 56.0, 41.2, 39.1, 37.3, 27.9, 25.7, 24.8.- MS (70 eV): *m/z* (rel. intensity): 208 (100, $[M^+]$), 190 (21), 178 (10), 148 (17), 149 (35), 138 (32), 136 (18), 135 (30), 134 (29), 133 (13), 131 (17), 130 (17), 122 (22), 121 (11), 107 (21), 106 (10), 105 (10), 92 (24), 79 (26), 67 (32), 55 (26).

(*E*)-**2**: IR: 3028, 2996, 2951, 2920, 2873, 1737, 1717, 1458, 1446, 1370, 1267, 1228, 1157, 1135, 1010, 981.- ^1H NMR (300 MHz, $CDCl_3$): δ 5.23-5.27 (m, 2H), 4.81 (dt, 1H, *J* = 5.6, 10.5), 3.86 (m, 1H), 2.85 (d, 1H, *J* = 10.5), 2.58 (d, 1H, *J* = 13.7), 2.07-2.44 (m, 6H), 1.71-1.84 (m, 2H), 1.43-1.58 (m, 2H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.8, 173.9, 133.9, 128.0, 62.8, 57.3, 42.0, 41.4, 37.2, 34.0, 32.9, 29.1.- MS spectrum as above.-$C_{12}H_{16}O_3$ (208.25): *calcd.* C 69.21, H 7.74; *found* C 69.09, H 7.67.