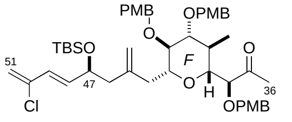
[28] A range of yields have been reported for this challenging Wittig step (Evans: 64%; Kishi: 40%; Smith: 34%) under a variety of reaction conditions.

[29] I. Paterson, C. J. Cowden, V. S. Rahn, M. D. Woodrow, *Synlett* **1998**, 915. In the model tris-PMB ether system A, we encountered competing oxidation by DDQ of the side chain to the chlorodienone: However, a similar deprotection of a bis-PMB ether was achieved without difficulty in the Kishi synthesis.[7b]



A

[30] A similar result was observed by the Kishi group.[7b]

[31] a) G. Jou, I. Gonzalez, F. Albericio, P. Lloyd-Williams, E. Giralt, *J. Org. Chem.* **1997**, *62*, 354; b) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, H. Vorbrüggen, *J. Am. Chem. Soc.* **1966**, *88*, 852.

[32] For a related regioselective macrolactonization employed for swinholide A, see: I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, S. Lamboley, *Tetrahedron* **1995**, *51*, 9467.

[33] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[34] Purity was determined by reverse-phase HPLC. Prodigy C_{18} 4.6 × 250 mm, 5 μm analytical column; 27.5% H_2O/MeOH; 1 mL min^{-1}.

[35] See Supporting information for tabulated ^{1}H and ^{13}C NMR data and copies of spectra.

[36] We thank Professors Pettit and Kishi for kindly providing comparison NMR spectra.

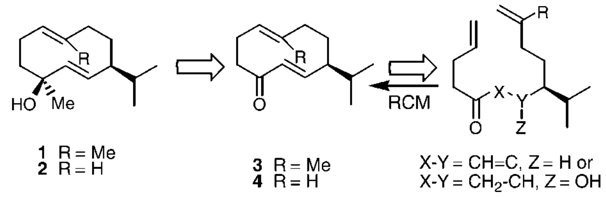
[37] Isolation from sponge sources: At present, we have synthesized 4.5 mg of **1** and 60 mg of its direct precursor **36**; optimum conditions for the final deprotection step are being developed. 13.8 mg from 400 kg of *Spongia* sp. by Pettit et al.[3a] + 7.6 mg from 112 kg of *Hyrtios altum.* by Kobayashi et al.[2c]

Synthesis of a 10-Membered Carbocycle By Olefin Metathesis**

Marta Nevalainen and Ari M. P. Koskinen*

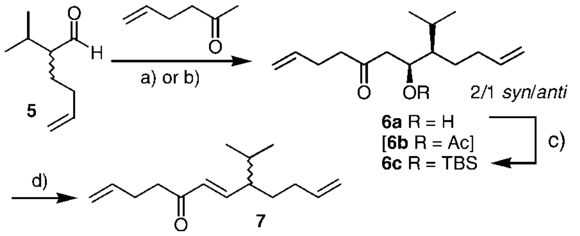
Dedicated to Professor Henry Rapoport

The pine sawfly *Neodiprion sertifer* is a common pest in pine trees of the northern hemisphere.[1] The population of larvae can cause extensive defoliation, resulting in serious economical damage. Therefore, great effort has recently been directed to monitor and control the population of sawfly species.[2] It was shown that the resin secreted by pines interferes with the development of larvae.[3] The main component of the sesquiterpene fraction of the resin of *Pinus sylvestris* is 1,6-germacradien-5-ol (**1**),[4] first isolated by Bohlmann et al.[5] from *Senecio phonolithicus.* On the other hand, 4α-hydroxygermacra-1(10),5-diene (4α-HDG, **2**) is a predominant foliage sesquiterpene in many pine trees (*Pinus radiata*).[6] To date, no synthesis for **1** or **2** has yet been reported.[7] Here we describe the synthesis of cyclodecenones (±)-**11** and (±)-**12**, which are direct precursors for (±)-**2** (Scheme 1), by ring-closing olefin metathesis (RCM). To the best of our knowledge, this is the first 10-membered carbocycle obtained by using the RCM methodology.[8] Only a few examples of the formation of ten-membered rings by RCM have been reported,[9] and all dealt with the synthesis of oxa- or azacycles.



Scheme 1. Retrosynthesis of 1,6-germacradien-5-ols **1** and **2**.

Among the many cyclization reactions, olefin metathesis has emerged as a very powerful tool for the formation of C=C bonds.[9, 10] However, as a result of inherent ring strain, the formation of 8- to 11-membered rings is particularly difficult,[9] and its success depends on the substitution pattern of the bis-olefin.[11] The importance of restricted chain mobility is clearly illustrated by **6a** (Scheme 2), in which the conformational-control element is the aldol moiety. Conversion of this functional group into an enone completely inhibits the cyclization, as described hereafter.



Scheme 2. Synthesis of bis-olefins **6** and **7**. a) LDA, THF, −78 °C (61%); b) LDA, THF, −78 °C; then Ac_2O (not isolated); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (96%); d) DBU, THF, 0 °C (56% from **5**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Aldehyde **5** was synthesized in 72% overall yield from isovaleric acid. Condensation of **5** with 5-hexen-1-one delivered aldol **6a** with 3,4-*syn*/3,4-*anti* (Felkin) selectivity. In situ entrapment of **6a** with acetic anhydride followed by DBU-promoted elimination yielded enone **7** (Scheme 2).

The RCM reaction of enone **7** in the presence of the Grubbs catalyst provided only oligomers, along with unconverted starting material (Table 1, entry 1). In CH_2Cl_2 solution, enone **7** adopts a linear conformation in which the olefinic termini are located at a maximum distance from each other. Therefore, only acyclic diene metathesis polymerization takes place. We were thus pleased to observe that the aldol **6a** (*syn*/*anti* 2/1) underwent the RCM reaction to form 10-membered

---

[*] Prof. A. M. P. Koskinen, Dr. M. Nevalainen
Laboratory of Organic Chemistry, Department of Chemical Technology
Helsinki University of Technology, 02015 HUT, Finland
Fax: (+358) 9-451-2538
E-mail: ari.koskinen@hut.fi

[**] Financial support has been provided by the Academy of Finland and HUT.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

Table 1. RCM reactions conducted on bis-olefins **6** and **7**.[a]

Entry	Bis-olefin	Catalyst (mol%)	Additive (mol%)	t [h]	Product (%)[b]	Recovered bis-olefin [%][b]
1	**7**	10	–	48	–	62
2	**6a**	15	–	48	**8** (11)	25
3[c]	**6a**	15	Me_2AlCl (100)	96	**9** (34)	30
4[d]	**6a**	10	Me_2AlCl (100)	96	**4** (32) **7** (28) **10** (7)	–
5	**6c**	10	–	48	**11** (35) **12** (16) **13** (11)	6
6	**6c**	10	Ti(O*i*Pr)$_4$ (10)	48	**11** (47) **12** (21) **13** (8)	–

[a] All reactions were performed in CH_2Cl_2 at reflux ($c = 0.56$ mM). [Ru]-carbene (Grubbs catalyst) was added with a cannula as a solution in CH_2Cl_2. [b] Yields of isolated products. [c] Reaction quenched with 1N HCl. [d] The reaction mixture was treated with DBU (100 mol%) before quenching.

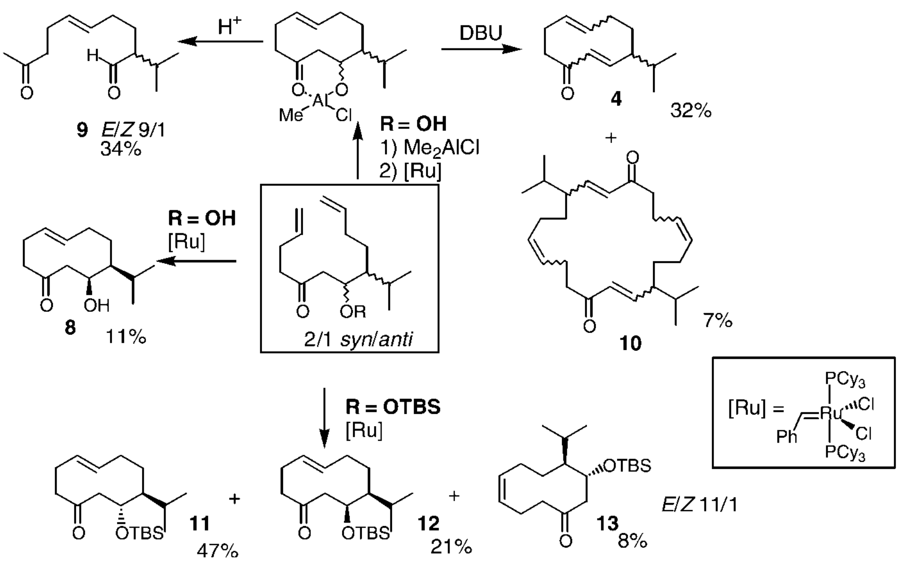
carbocyle **8** (Scheme 3). The *E-cis* ring was formed exclusively (the *cis* configuration of this isomer was assigned by analogy of its NMR data with that obtained for **13**; see below), but unfortunately in only 11% yield (Table 1, entry 2). Unconverted starting material was recovered in 25% yield, and the formation of oligomers was also observed. The reverse reaction of the free hydroxy group with the catalyst competes with the desired metathesis. Moreover, the hydroxy group is not large enough to template the bis-olefin towards ring closure.

In view of those results, we decided to treat aldol **6a** with an equimolar amount of Me_2AlCl and attempt the RCM reaction on the resulting metal complex (Scheme 3).[13] We observed that the RCM reaction proceeded to form the target macrocycle. However, the drawback of this approach turned out to be the quenching of the reaction. Treatment of the reaction mixture with dilute hydrochloric acid gave retroaldol product **9** in 34% yield as a 9/1 *E*/*Z* mixture of diastereomers (Table 1, entry 3). The remainder consisted of oligomers and unconverted starting material (30% recovery yield). Clearly, the retroaldol reaction occurred to release the transannular strain of the newly formed 10-membered ring. When the reaction mixture was treated under reflux with DBU (100 mol%) for 1 h, cyclic enone **4** (mixture of diastereomers) was obtained as an inseparable mixture along with acyclic enone **7** (Table 1, entry 4). The 20-membered enone **10** was isolated as a side product in 7% yield and as a diastereomeric mixture.

In light of these results, protection of the hydroxy group of aldol **6a** was envisaged as a possible solution. Indeed, *O*-TBS-protected bis-olefin **6c** (*syn*/*anti* 2/1) underwent the RCM reaction smoothly and provided 10-membered rings **11**–**13** in 62% total yield (Table 1, entry 5). Unconverted starting material was recovered in 6% yield. Careful inspection of the ^1H NMR spectrum of the crude reaction mixture revealed that only three of the four possible diastereomers were formed and that the *E*/*Z* ratio was 8/1. We tentatively assigned[12] the relative C8,C9 configuration of the *Z* isomer (**13**) and of the major *E* isomer (**11**) to be *trans*. Both compounds showed similar spectral patterns for the characteristic signals. In contrast, the minor *E* isomer should have the *cis* configuration for those stereocenters. It can be concluded that both *syn* and *anti* aldols favor the formation of the *E* olefin. However, as the recovered bis-olefin was enriched in the *anti* isomer (1/3 *syn*/*anti* mixture), the *syn* aldol (leading to *trans* rings) must cyclize faster than the *anti* aldol. The *anti* aldol (leading to the *cis* ring) decomposes partially by oligomerization.

Finally, when the RCM reaction of **6c** was conducted in the presence of 10 mol% of Ti(O*i*Pr)$_4$, the total yield of the cyclization increased to 76% and the *E*/*Z* ratio to 11/1 (Table 1, entry 6). Coordination of the Lewis acid to the carbonyl group of **6c**[13] seems to confer further conformational restriction on the bis-olefin and thus favors the desired cyclization.

In summary, we have successfully synthesized (±)-9-(*tert*-butyldimethylsilyloxy)-8-isopropylcyclodec-4-enone as an 11:1 mixture of *E*/*Z* diastereomers in 76% yield by using the binary system Grubbs catalyst/Ti(O*i*Pr)$_4$. This is the first example of a 10-membered carbocycle being formed by RCM. The bulky TBS group acts as a conformational-control element that facilitates ring closure.[11]



Scheme 3. RCM reactions of aldol **6a** and silylated aldol **6c**.

Received: June 1, 2001 [Z17217]

---

[1] M. Wagner, K. F. Raffa, *Sawfly Life Story: Adaptation to Woody Plants*, Academic Press, San Diego, **1993**.

[2] PHERODIP *Pine Sawfly Pheromones for Sustainable Management of European Forest*, European Community contract no. FAIR1-CT95-0339, Final Report.

[3] S. Larsson, C. Björkman, R. Gref, *Oceologia* **1986**, *70*, 77–84.

[4] G. Bergström, A.-B. Wassgren, G. Birgersson, *Acta Chem. Scand.* **1994**, *48*, 187–188.

[5] F. Bohlmann, K.-H. Knoll, C. Zdero, P. Mahanta, M. Grenz, A. Suwita, D. Ehlers, N. L. Van, W.-R. Abraham, A. A. Natu, *Phytochemistry* **1977**, *16*, 965–985.

[6] a) F. Bohlmann, C. Zdero, D. Berger, A. Suwita, P. Mahanta, C. Jeffrey, *Phytochemis-*

try **1979**, *18*, 79–93; b) L. G. Cool, E. Zavarin, *Biochem. Syst. Ecol.* **1992**, *20*, 133–144.

[7] For a first attempt, see O. Nordin, PhD thesis, Kungl. Tekniska Högskolan, Stockholm, Sweden, **1999**.

[8] For 7- to 9-membered carbocycles, see a) M. E. Maier, *Angew. Chem.* **2000**, *112*, 2153–2157; *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077; b) J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *Org. Lett.* **2000**, *2*, 3209–3212. c) H. Tang, N. Yusuff, J. L. Wood, *Org. Lett.* **2001**, *3*, 1563–1566.

[9] A. Fürstner, K. Radkowski, *Chem. Commun.* **2001**, 671–672, and references therein.

[10] a) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; b) T. M. Trnka, R. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29.

[11] a) S. D. Edwards, T. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4267–4270; b) D. Bourgeois, J. Mahuteau, A. Pancrazi, S. P. Nolan, J. Prunet, *Synthesis* **2000**, 869–882.

[12] On the basis of the different reactivity of **11**–**13** towards DBU to form enone **4**. The minor isomer of the *E* rings **12** eliminates OTBS in the presence of DBU (DMF, 100°C, 5 h) much faster than the other isomers (**11** and **13**). On the basis of molecular models, the H7 protons are much more accessible to the bulky base if the *i*Pr and TBSO groups are disposed *cis* to each other. In the case of the *trans* isomer, the rate of proton abstraction is then much lower due to steric hindrance. Corroboration of this hypothesis would require a complete computational study to aid the full interpretation of the spectroscopic data of **11**–**13**. For a related example, see G. P.-G. Hareau, M. Koiwa, S. Hikichi, F. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 3640–3650.

[13] This is the first example of the use of a metal chelate as a conformational-control element to favor cyclization. Coordination complexes of the type C=O ··· Ti(O*i*Pr)$_4$ have been used for the same purpose: a) A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136; b) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* **2001**, *66*, 81–88.

Experimental Detection of Tetraoxygen[**]

Fulvio Cacace,[*] Giulia de Petris, and Anna Troiani

The search for tetraoxygen, which dates back to a study by Lewis in 1924,[1] is being actively pursued, owing to its fundamental interest, its potential role as a material of high energy density,[2] and, in particular, the current upsurge of interest in excited states of O_2 with relevance to atmospheric chemistry and to terrestrial and Venusian nightglow.[3] Numerous calculations at different levels of theory predict the existence of metastable O_4 molecules with a D_{2d} cyclic geometry[4] or a D_{3h} "pinwheel" geometry.[5, 6] Positive experimental detection of such species has not been reported, whereas weakly bonded $(O_2)_2$ van der Waals dimers, with dissociation enthalpies of less than 1 kcal mol^{-1}, have long been known and thoroughly characterized.[7] Indirect evidence for metastable tetraoxygen was derived from experiments involving electron transfer from Cs to O_4^+, followed by the measurement of the kinetic energy spectrum of the O_2 fragments. The structure of the kinetic energy distribution was consistent with the intervention of some O_4 species that were not observable under the conditions of the experiment.[8] Strong evidence for metastable O_4 was derived from studies involving the photoionization of O_2 excited by a DC discharge.[9, 10] Interestingly, the results of both experimental studies were interpreted as suggestive of the existence of a third metastable O_4 species in addition to the theoretically predicted molecules, namely, a relatively long lived complex between a ground-state O_2 molecule and an O_2 molecule in the excited $c^1\Sigma_u^-$ electronic state.[10]

To obtain conclusive proof, we have carried out an experiment aimed at detecting intact O_4. Our approach is also based, like previous studies,[8] on the neutralization of O_4^+ cations in the gas phase, but uses for the identification of the intact O_4 molecule neutralization reionization (NR) mass spectrometry[11] on a highly sensitive instrument that allowed the detection of other elusive atmospheric species, such as hydrogen trioxide[12] and the $[H_2O^+\cdot O_2^-]$ charge-transfer complex.[13]

The O_4^+ ions were generated in a chemical ionization (CI) source by association of O_2 molecules with O_2^+ primary ions, formed both in the $X^2\Pi_g$ ground state and in electronically excited states by electron impact.[14] The ions were then accelerated through 4–8 keV, magnetically mass resolved, and probed by collisionally activated dissociation (CAD) mass spectrometry. Whereas the CAD spectrum of $^{16}O_4^+$ from the ionization of $^{16}O_2$ shows $^{16}O_2^+$ as the charged fragment, $^{16}O_2{}^{18}O_2^+$ ions from $^{16}O_2/^{18}O_2$ mixtures give $^{16}O_2^+$ and $^{18}O_2^+$ without the $^{16}O^{18}O^+$ ions[15] that would suggest isotopic scrambling (Figure 1). This shows that the O_4^+ ions probed contain two discrete O_2 units, each of which retains its original identity.

In the NR experiments the O_4^+ ions were also accelerated to 4–8 keV and mass-selected before undergoing two consecutive collision events in separate cells aligned along the beam path. In the first cell a fraction of the ions undergoes electron transfer from a target gas to yield O_4 together with neutral and charged fragments. All O_4^+ parent cations that escaped neutralization and any charged fragments were removed by a deflecting electrode, so that a beam containing only fast neutral species entered the second cell, where reionization by collision with a suitable target gas gives cations that are energy-selected, and their mass spectra are recorded. Detection of a "recovery" peak, that is, of a charged species with the same m/z ratio as the original O_4^+ ions demonstrates the occurrence of the sequence of Equation (1) and hence the existence of a neutral O_4 species with a lifetime that exceeds the flight time from the neutralization to the reionization cell.

$$O_4^+ \xrightarrow[\text{Neutralization}]{+M,\ -M^+} O_4 \xrightarrow[\text{Reionization}]{-e} O_4^+ \qquad (1)$$

The NR spectra of the $^{16}O_4^+$, $^{16}O_2{}^{18}O_2^+$, and $^{18}O_4^+$ ions, illustrated in Figure 2, show significant recovery peaks at $m/z = 64$, 68, and 72, respectively, a result that positively

---

[*] Prof. Dr. F. Cacace, Prof. Dr. G. de Petris, Dr. A. Troiani
Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive
Università di Roma "La Sapienza"
P.le Aldo Moro, 5, 00185 Roma (Italy)
Fax: (+390) 6-4991-3133
E-mail: fulvio.cacace@uniroma1.it

[**] This work was supported by the University of Rome, the Italian National Research Council (CNR), and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

0044-8249/01/11321-4186 $ 17.50+.50/0