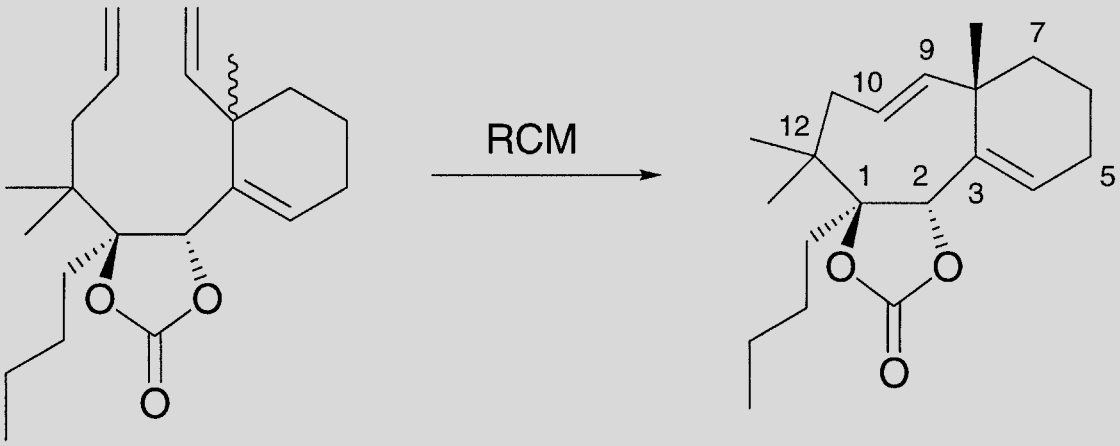
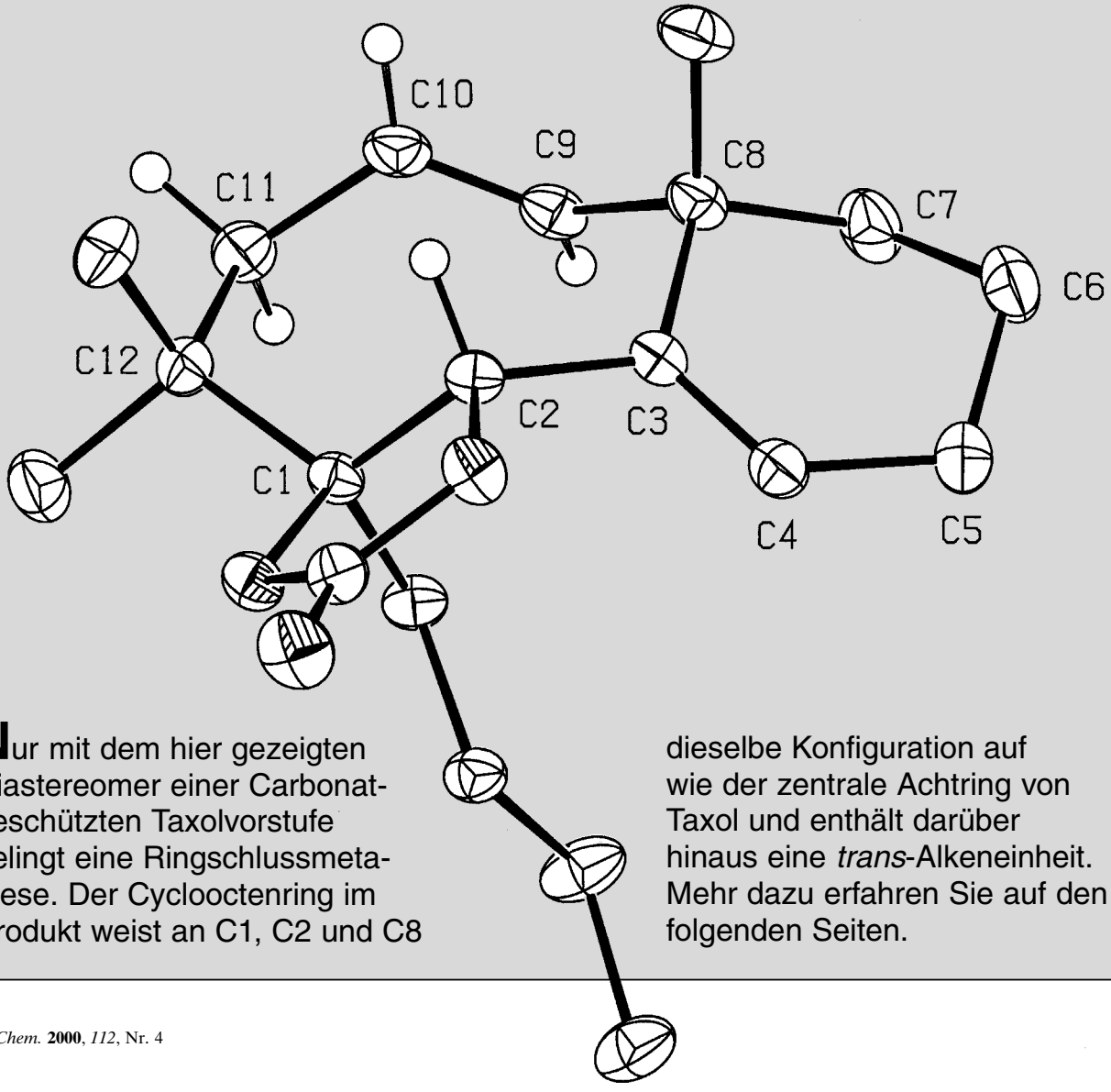
Das erste durch Ringschlussmetathese (RCM) synthetisierte *trans*-Cycloocten



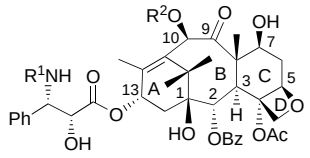


Nur mit dem hier gezeigten Diastereomer einer Carbonat-geschützten Taxolvorstufe gelingt eine Ringschlussmetathese. Der Cyclooctenring im Produkt weist an C1, C2 und C8 dieselbe Konfiguration auf wie der zentrale Achtring von Taxol und enthält darüber hinaus eine *trans*-Alkeneinheit. Mehr dazu erfahren Sie auf den folgenden Seiten.

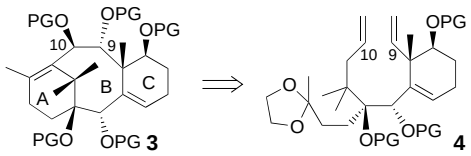
Synthesis of Highly Functionalized Cyclooctenes by Ring-Closing Metathesis: Unexpected Formation of a *trans* Isomer**

Damien Bourgeois, Ange Pancrazi, Louis Ricard, and Joëlle Prunet*

During our studies towards the synthesis of the antitumor agents taxol (**1**)[1] and taxotere (**2**)[2] we explored several convergent routes.[3] One of them relies on a ring-closing metathesis (RCM) to form the eight-membered cycle of this molecule (Scheme 1). This reaction has become a powerful



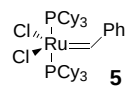
1 Taxol (paclitaxel) $R^1 = C_6H_5CO$, R^2 = Ac
2 Taxotere (docetaxel) $R^1 = t$BuOCO, R^2 = H



Scheme 1. Retrosynthesis of the ABC ring-system of taxol. See ref. [8] for abbreviations.

tool in organic synthesis, since it involves nonfunctionalized olefins that are usually unreactive towards classical reagents, and is compatible with diverse functional groups.[4] To the best of our knowledge there are only four reports in the literature of such a reaction for the synthesis of carbocyclic rings of this size.[5] Herein we present cyclizations of highly functionalized precursors of the BC ring-system of taxol using the Grubbs' ruthenium catalyst **5**[6] or Schrock's molybdenum catalyst **6**[7], and also the unexpected formation of a *trans*-cyclooctene in one case.

The closure of the B-ring of taxol between C9 and C10 by RCM presents a double challenge; the high activation enthalpy for the formation of an eight-membered ring has to be overcome, and the neopentylic position at C8 adjacent to one of the olefinic partners might hamper the formation of the intermediate metallacyclobutane, which is already fused



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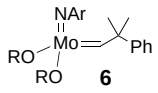
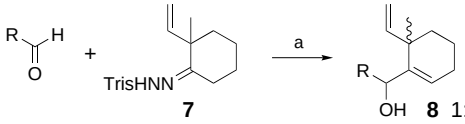


6

Cy = Cyclohexyl

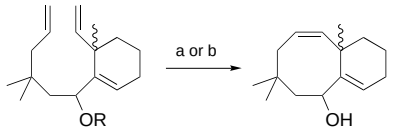
Ar = 2,6-*i*PrC$_6$H$_5$
R = (CF$_3$)$_2$(CH$_3$)C

to a highly substituted eight-membered ring. We therefore designed a short route to metathesis precursors **8**, which were synthesized as 1:1 mixture of diastereomers by using a Shapiro reaction on trisylhydrazone **7** and quenching with the appropriate aldehyde (Scheme 2).[9]



Scheme 2. Preparation of the metathesis precursors. a) 2.1 equiv *t*Buli, THF, −78 °C, 30 min; 0 °C, 1 min; 1.2 equiv RCHO, −78 °C.

Attempts of ring-closure on alcohol **9** only led to polymers. However, formation of an eight-membered ring was observed when the triethylsilyl ether derivative **10** was heated for eight days in benzene in the presence of the ruthenium complex **5** (Scheme 3). For purification purposes the TES ether was



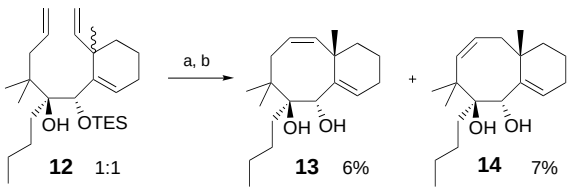
9 R = H
10 R = TES

11 a 20% b 85%

Scheme 3. Formation of a cyclooctene. a) 10% **5**, 0.02 M, benzene, 80 °C, 6 d; TBAF · 3 H$_2$O, THF; b) 10% **6**, 0.02 M, benzene, 80 °C, 3 d; TBAF · 3 H$_2$O, THF.

cleaved and alcohol **11** was then obtained in 20% yield as a single diastereomer, whose stereochemistry has not been determined. A Thorpe–Ingold effect of the TES group could explain the difference in yields between **9** and **10**,[10] but a complexation of the catalyst by the free OH group in **9** cannot be excluded. A much better yield was obtained for the RCM reaction with Schrock's catalyst, which gave both diastereomers of **11**.

We then decided to check the feasibility of the RCM using more elaborate models such as alcohol **12**, where the steric hindrance is similar to that of the precursor **4**, a potential precursor for the synthesis of the ABC tricycle (Scheme 4). We assumed that additional substituents would favor the cyclization by reducing the conformational freedom of the molecule. However, reaction of **12** with the ruthenium



12 1:1 **13** 6% **14** 7%

Scheme 4. RCM with a more elaborate model. a) 10% **5**, 0.02 M, benzene, 80 °C, 8 d; b) TBAF · 3 H$_2$O, THF.

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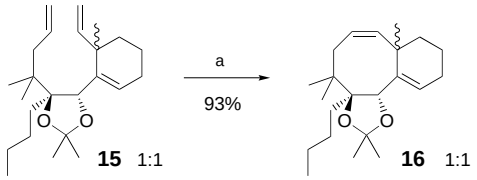
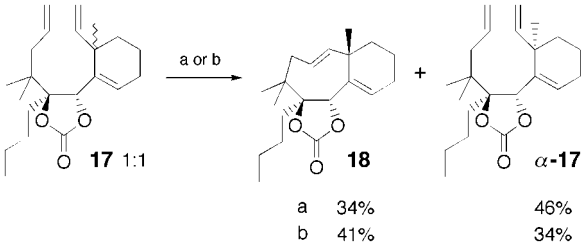
complex **5** in benzene at reflux for eight days produced only minor amounts of two cyclized products.[11] Removal of the TES ether led to the expected product **13** as a single diastereomer[12] together with **14**, in which the double bond has shifted from C9-C10 to C10-C11. The struture of **14** was determined by X-ray diffraction analysis.[13] A similar isomerization was reported by Taylor et al.[10, 16]

Simple semi-empirical calculations (MM2/PM3) on **12** clearly showed that the substituents at C1 forced the diene in a ground-state conformation in which the two double bonds are far apart. However, a cyclic protecting group as in **15** appeared to place the two olefin residues at a reasonable distance for a metathesis reaction. We were thus disappointed to find only traces of the desired cyclooctene in the unpurified reaction mixture when the Grubbs' catalyst was employed with acetonide **15**, even after eight days in benzene at reflux (Scheme 5). However, RCM reaction of **15** with Schrock's molybdenum catalyst **6** led to cyclooctene **16** in 93% yield. Three days were necessary to drive the reaction to completion, but conversion of both isomers was total, giving a 1:1 mixture of diastereomeric cyclooctenes **16** that were easily separable by flash chromatography. Their structures were determined by extensive NMR studies.[17]



Scheme 5. RCM of compounds bearing an acetonide at C1-C2. a) 10% **6**, 0.02 M, benzene, 80 °C, 3 d.

Another suitable protecting group for the C1-C2 diol of taxol precursors such as **3** is a cyclic carbonate.[18] We thus submitted compound **17** to the Grubbs catalyst **5** in benzene at reflux for 8 days (Scheme 6). Surprisingly, only one diastereomer underwent cyclization, and the resulting product **18** was a *trans*-cyclooctene produced in 34% yield (68% based



Scheme 6. Synthesis of a *trans*-cyclooctene. a) 10% **5**, 0.02 M, benzene, 80 °C, 8 d; b) 10% **6**, 0.02 M, benzene, 80 °C, 3 d.

on the diastereomeric ratio of the starting diene). The other diastereomer of **17** was recovered in 46% yield. The same reaction with the molybdenum catalyst produced 41% of cyclic product **18**, along with 34% of recovered **17** (bearing an α-methyl group at C8).

Structural evidence for **18** was obtained by X-ray diffraction studies[13] (Figure 1). A coupling constant of 16.7 Hz is observed between the two olefinic protons at C9 and C10 in

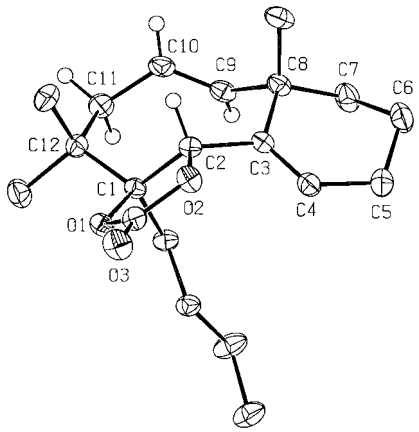


Figure 1. Platon representation of *trans*-cyclooctene **18**.[19] For the purpose of clarity only the hydrogen atoms on the eight-membered ring are shown.

the ^{1}H NMR spectrum.[20] A C8-C9-C10-C11 torsion angle of 139.3° in the solid-state structure indicates a loss of the π character of the double bond. All the stereocenters in **18** (C1, C2, C8) present the configuration required for the synthesis of taxol. Moreover, **18** is the first *trans*-cyclooctene obtained by olefin metathesis. This result is totally unexpected, as olefin metathesis is thought to occur exclusively under thermodynamic control.[21] In our case, no trace of the more stable corresponding *cis*-cyclooctene was detected. A complexation of the catalyst by the carbonyl moiety might be invoked,[22] although the involved chelate would be an eight-membered ring. Further studies to provide an explanation of this result are underway.

In conclusion, we have shown that highly functionalized cyclooctenes can be synthesized in very good yields with Grubbs' or Schrock's catalyst. In the specific case of carbonate **17**, only one diastereomer cyclized to give cyclooctene **18**, which not only possesses the required stereochemistry for the C1, C2, and C8 centers of taxol, but also presents a *trans* olefin. This result indicates that RCM does not proceed to complete thermodynamic equilibrium in this case.

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[8] Abbreviations: Ac = acetate; Bz = benzoate; PG = protecting group; Tris = 2,4,6-triisopropylphenylsulfonyl; TES = triethylsilyl; TBAF = tetrabutylammonium fluoride.

[9] A detailed analysis of the synthesis of the metathesis precursors will be reported elsewhere.

[10] S. D. Edwards, T. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4267 – 4270.

[11] Schrock's molybdenum catalyst was not used with **12**, as it is known to be incompatible with free OH groups.

[12] The stereochemistry of **13** was determined by correlation with (*Z*)-**18**, whose synthesis will be reported elsewhere.

[13] X-ray structure data: Nonius KappaCCD diffractometer, ϕ and ω scans, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, $T = 150$ K, structure solution with maXus,[14] refinement against F^2 (SHELXL-97[15]) with anisotropic thermal parameters for all non-hydrogen atoms, hydrogen positions were calculated with riding isotropic thermal parameters. Data collection for **14**: crystal dimensions $0.20 \times 0.20 \times 0.20$ mm^3, monoclinic, space group $P2_1/c$, $a = 8.7890(3)$, $b = 20.7820(3)$, $c = 9.9300(8)$ Å, $\alpha = 90.0000(19)$, $\beta = 107.7280(16)$, $\gamma = 90.0000(19)^\circ$, $V = 1727.61(15)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.124$ g cm^{-3}, $\mu = 0.070$ cm^{-1}, $F(000) = 648$, $\theta_{max} = 27.48^\circ$, h, k, l ranges: 0 11, 0 26, −12 12, 3958 data collected, 3958 unique data ($R_{int} = 0.025$), 3378 data with $I > 2\sigma(I)$, 196 parameters refined, GOF(F^2) = 1.058, final R indices ($R_1 = S||F_o| - |F_c||/S|F_o|$, $wR_2 = [Sw(^2_o - F^2_c)^2/Sw(F^2_o)^2]^{1/2}$): $R_1 = 0.0425$, $wR_2 = 0.1083$, max./min. residual electron density 0.266(0.038)/−0.180(0.038) e A^{-3}. Data collection for **18**: crystal dimensions $0.20 \times 0.20 \times 0.20$ mm^3, monoclinic, space group $P2_1/c$, $a = 8.4850(4)$, $b = 15.6940(5)$, $c = 13.9450(7)$ Å, $\alpha = 90.000(3)$, $\beta = 106.2550(18)$, $\gamma = 90.000(3)^\circ$, $V = 1782.73(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.186$ g cm^{-3}, $\mu = 0.078$ cm^{-1}, $F(000) = 696$, $\theta_{max} = 30.03^\circ$, $-11 \le h \le 9$, $-22 \le k \le 14$, $-12 \le l \le 19$, 10513 data collected, 5193 unique data ($R_{int} = 0.036$), 4160 data with $I > 2\sigma(I)$, 212 parameters refined, GOF($F2$) = 1.038, final R_{ind}: $R_1 = 0.0475$, $wR_2 = 0.1320$, max./min. residual electron density 0.431(0.046)/−0.396(0.046) e A^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-135213 and 135214. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[16] The authors invoke an acid catalysis resulting from the use of dichloromethane as solvent, since the presence of triethylamine inhibits the formation of the isomerized product. In our case, the isomerization might result from the prolonged exposure of the product to the catalyst at high temperature: Grubbs observed isomerization of RCM products during distillation when residual amounts of the catalyst were present, see H. D. Maynard, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 4137 – 4140.

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[20] Selected data for **18**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.01$ (ddd, $J = 5.0, 2.5, 1.5$ Hz), 5.80 (ddd, 1H, $J = 16.7, 12.0, 3.5$ Hz), 5.39 (d, 1H, $J = 16.7$ Hz), 5.09 (d, 1H, $J = 2.5$ Hz), 2.27 (t, 1H, $J = 12.0$ Hz), 2.25 – 2.18 (m, 1H), 2.10 (dd, 1H, $J = 12.0, 3.5$ Hz), 2.11 – 2.01 (m, 1H), 1.88 – 1.81 (m, 3H), 1.76 – 1.68 (m, 2H), 1.65 – 1.56 (m, 2H), 1.28 (d, 3H, $J = 0.4$ Hz), 1.22 (s, 3H), 1.17 (s, 3H), 0.89 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 154.2, 142.3, 137.5, 126.7, 125.4, 93.2, 82.7, 48.2, 43.4, 41.8, 36.2, 31.7, 26.2, 26.0, 24.8, 23.0, 22.0, 20.4, 17.6, 13.8$.

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Diastereoselective Pinacol Coupling Reactions of α-Ketoamides Mediated by SmI_2: Synthesis of Enantiomerically Pure *R* and *S* Quaternary Tartaric Acids**

Sam Min Kim, Il Suk Byun, and Yong Hae Kim*

Multidentate, chiral, C_2-symmetric ligands are well-known for their ability to impart asymmetry to transition and main group elements.[1] C_2-Symmetric diols are among the most frequently applied examples of such molecules, especially in the area of asymmetric catalysis.[2] Most diol ligands have been derived from C_2-symmetric molecules which occur naturally in optically pure form (such as tartaric acid).[2] However, the number of chiral precursors available from natural products is seriously limited.

The pinacol coupling was first described a long time ago,[3] but this reaction is still a versatile tool for chemists. The intermolecular coupling of various aldehydes or ketones to the corresponding pinacols has been extensively studied.[4] However, pinacols in an enantiopure form have not really been obtained using this type of coupling.[5] Although the asymmetric dihydroxylation of olefins mediated by osmium tetroxide has become one of the most useful methods for the preparation of C_2-symmetric diols,[6] asymmetric dihydroxylations of tetrasubstituted olefins are extremely rare[7a] and give low enantioselectivity.[7]

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