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Selective cyclopropylcarbinyl rearrangement of tricyclo[5.3.1.0]undecanols induced by pyridinium chlorochromate

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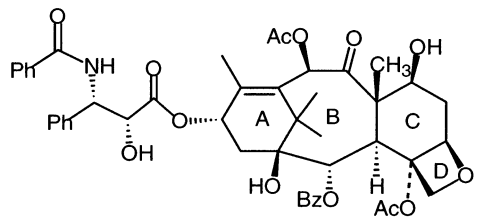
Abstract—Tricyclo[5.3.1.0]undecanols were transformed to bicyclo[5.3.1]undecanols in good yield by using pyridinium chlorochromate.

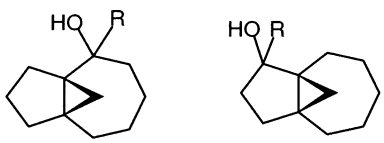
The bicyclo[5.3.1]undecanol ring system is present in naturally occurring taxanes and particularly in anticancer drugs such as taxol.[1]



Taxol

Here, we report an easy access to the synthesis of the AB ring system of taxol which allows the functionalization of the eight- or six-membered ring. Although the cyclopropylcarbinyl rearrangement of bicyclic systems[2–6] has been extensively studied, the cyclopropylcarbinyl rearrangements of tricyclic systems are rare.[7–10] We investigated cyclopropylcarbinyl rearrangement of tricyclo[5.3.1.0]undecanols of type **A** and **B** under oxidative conditions, e.g. with pyridinium chlorochromate (PCC) and under acidic conditions (10% aqueous HCl in THF: 1/1).

Tricyclo[5.3.1.0]undecanols **1a**/**1a**′ and **1b–e** were prepared from hydroazulenol **11** (Schemes 1 and 2) and the tricyclo[5.3.1.0]undecanols **4a**/**4a**′ and **4b**/**4b**′ were prepared from hydroazulenone **14** (Scheme 3). After treatment of 1,2-cyclohexanedione **7** with vinylmagnesium bromide (2 equiv., THF, 0°C), hydroxy ketone **8** was obtained (98% yield) and transformed to diol **9** (98% yield) as a mixture of two isomers in a ratio 46/54 by addition of vinylmagnesium bromide (2 equiv., THF, 0°C).[11] After thermolysis at 210°C, diol **9** was rearranged to hydroazulenone **10**[11] which was reduced to



A **B**

the corresponding alcohol **11** in 99% yield by using $NaBH_4$ (1 equiv.) in the presence of $CeCl_3{\cdot}7H_2O$ (1 equiv.) in MeOH. The obtained alcohol **11** was then treated with CH_2I_2 (6 equiv.) in the presence of Et_2Zn (3 equiv.) at −78°C and transformed to the cyclopropylcarbinols **1a** and **1a**′ (82%) as an inseparable 88/12 mixture.[12]

Compounds **1a** and **1a**′ could also be obtained by reduction of the tricyclo[5.3.1.0]undecanone **12**. A mixture of **1a** and **1a**′ was obtained in a ratio of 21/79 when $NaBH_4$ was used for the reduction and a ratio of 43/57 by using DIBAL-H (Scheme 2). For the synthesis of alcohols **1b–e**, ketone **12**[13] was treated with various Grignard reagents. The addition of vinylmagnesium bromide produced **1b**, as an inseparable 74/26 mixture, in 88% yield, whereas isopropylmagnesium bromide led to **1c** as a single isomer in 68% yield and while allylmagnesium bromide afforded alcohol **1d** as a single isomer in 86% yield. Oxidative cleavage of the allyl group present in **1d**, by using O_3 in 2.5 M methanolic NaOH,[14] afforded the methyl ester **1e** (Scheme 2).

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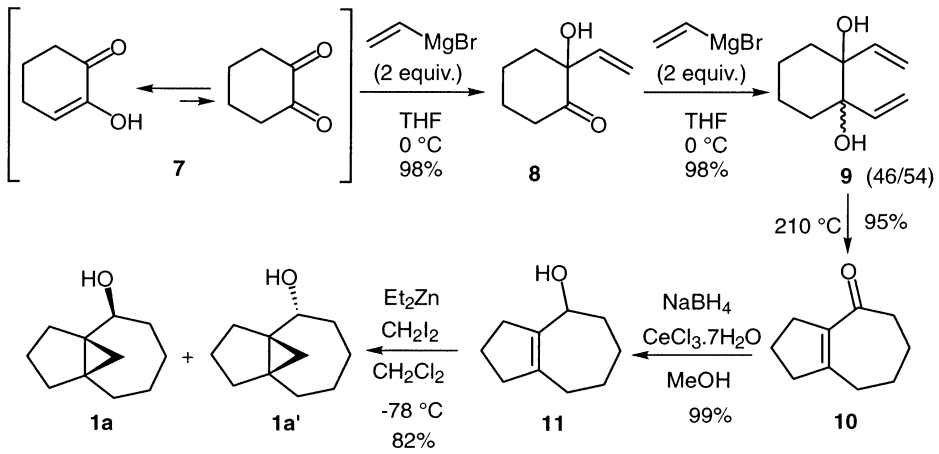
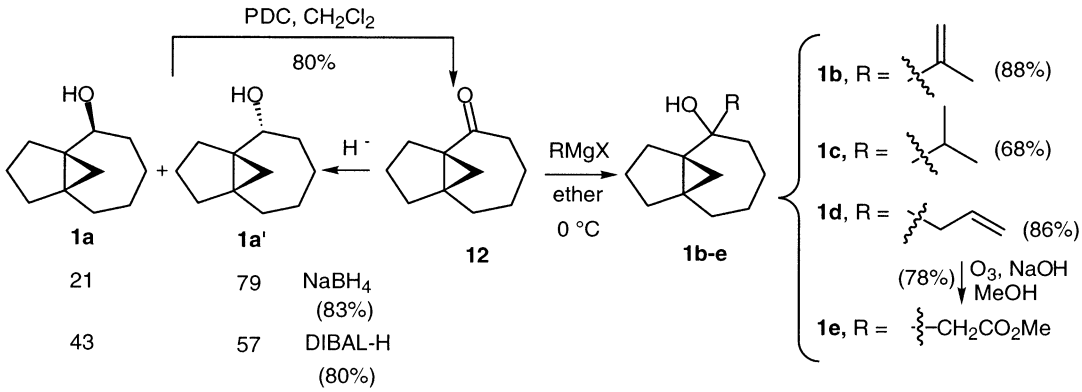


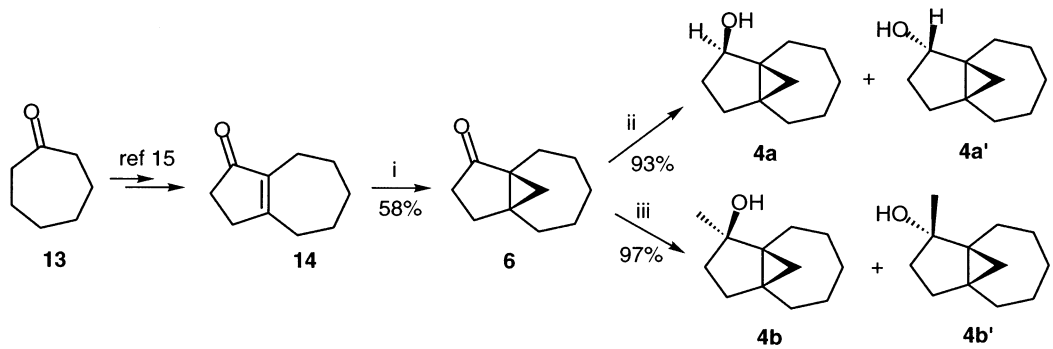
Scheme 1. Synthesis of **1a** and **1a**′.



Scheme 2. Synthesis of tricyclo[5.3.1.0]undecanols **1a**/**1a**′ and **1b–e**.

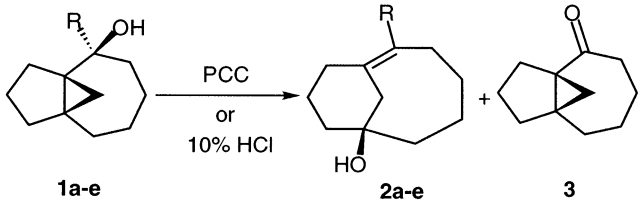
Cyclopropylcarbinols **4a** and **4a**′ were synthesized from cycloheptanone **13** which was transformed to hydroazulenone **14**[15] and subsequently converted to **6** by treatment with trimethysulfoxonium iodide.[16] Reduction of **6** with $NaBH_4$ in MeOH at room temperature led to the separable alcohols **4a** and **4a**′ as a 96/4 mixture in 93% yield. Reaction of **6** with methylmagnesium bromide afforded cyclopropylcarbinols **4b** and **4b**′ (ratio: 98/2, yield: 97%). Compound **4a** was purified by chromatography and characterized by ^1H NMR-NOE experiments[9b,17] (Scheme 3).

The rearrangement of tricyclo[5.3.1.0]undecanols **1a**/**1a**′, **1b–e**, **4a–b** were carried out with PCC[18] or 10% aqueous HCl in THF (1/1).[19] Cyclopropylcarbinols **1a**/**1a**′ afforded two compounds with PCC (3 equiv., CH_2Cl_2, rt): the rearranged product **2a**[20,21] and ketone **3**. These two products were easily separated by flash chromatography. It is worth noting that the ratio of **2a** and **3** depends on the ratio of **1a** and **1a**′. Under acidic conditions, **2a** was the only isolated product (87% yield) (Table 1). In the case of compounds **1b–e**, regardless of the conditions (PCC or HCl), the only products formed



Scheme 3. Synthesis of **4a**/**4a**′ and **4b**/**4b**′. (i) Trimethylsulfoxonium iodide, NaH, DMSO, 0°C; (ii) $NaBH_4$, MeOH/THF, 0°C; (iii) CH_3MgBr, ether, 0°C.

Table 1. Rearrangement of **1a**/**1a′**, **1b–e** by using PCC or 10% HCl in THF



1a-e **2a-e** **3**

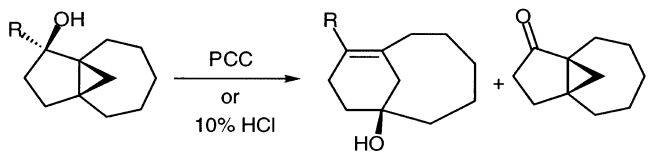
Starting material	PCC			10% HCl		
	T (°C), *t* (h)	**2** (Yield (%))	**3** (Yield (%))	*T* (°C), *t* (h)	**2** (Yield (%))	**3** (Yield (%))
1a/**1a′** = 88/12	rt, 0.5	48	40			
1a/**1a′** = 55/45	rt, 0.5	52	43	rt, 1	87	0
1a/**1a′** = 21/79	rt, 0.5	27	63			
1b	rt, 20	73	0	rt, 0.7	82	0
1c	rt, 0.5	85	0	rt, 0.3	94	0
1d	rt, 0.3	95	0	rt, 0.3	92	0
1e	rt, 24	72	0	rt, 0.5	78	0

were the rearranged products **2** in yields up to 70% (Table 1). The reactivity of alcohols **4a** and **4b** were also examined. When **4a** was treated with PCC (3 equiv., CH_2Cl_2, rt), ketone **6** was isolated in 80% yield. On the contrary, the rearranged product **5a** was obtained in 92% yield when **4a** was treated under acidic conditions. In the case of **4b**, PCC as well as acidic conditions led to the corresponding rearranged compound **5b** in up to 90% yield (Table 2).

The conversion of cyclopropylcarbinols to β,γ-unsaturated alcohols has been previously explained by the formation of intermediate cyclopropylcarbinyl cations under acidic conditions.[22] In the case of the secondary cyclopropylcarbinol **4a**, it seems that the weak acidity of PCC is not sufficient to induce the formation of a cyclopropylcarbinyl cation and, the oxidation process takes place to produce ketone **6**. As in compound **4b**, the *trans* periplanar arrangement of the C1–C7 and the C8–OCr bonds is not fulfilled, the rearranged product **5b** could not be the result of a concerted fragmentation process in which the initially formed chromic ester **II** will be the leaving group that will promote the cleavage of the C1–C7 bond of the cyclopropyl ring. As a tertiary carbocation is formed more easily than a secondary carbocation, the weak acidity of PCC can induce the formation of **5b** via intermediate **I** (ionic mechanism) (Scheme 4).

Contrary to the secondary cyclopropylcarbinol **4a** (R = H), which was transformed only to the oxidized product **6**, the treatment of **1a**/**1a′** with PCC led to a mixture of the rearranged compound **2a** and ketone **3**. The ratio of these products depended on the ratio of **1a**/**1a′**. A 55/45 mixture of **1a**/**1a′** produced **2a** and **3** in a ratio of 52/43, whereas a 21/79 mixture of **1a**/**1a′** led to **2a**/**3** in a ratio of 27/63 and a 88/12 mixture of **1a**/**1a′** led to a mixture of **2a**/**3** in a ratio of 48/40. In alcohol **1a**, where the *trans* periplanar arrangement of the C1–C7 and the C8–OCr bonds is fullfilled (cf. intermediate **III**), oxidation can compete with rearrangement and the rearranged product **2a** can be formed as well as ketone **3**. The rearrangement of **1a** by a stepwise mechanism (ionic) cannot be excluded. In the case of compound **1a′**, as the C1–C7 and the C8–OCr bonds are not *trans* periplanar (cf. intermediate **IV**), this com-

Table 2. Rearrangement of alcohols **4a** and **4b** by using PCC or 10% HCl in THF

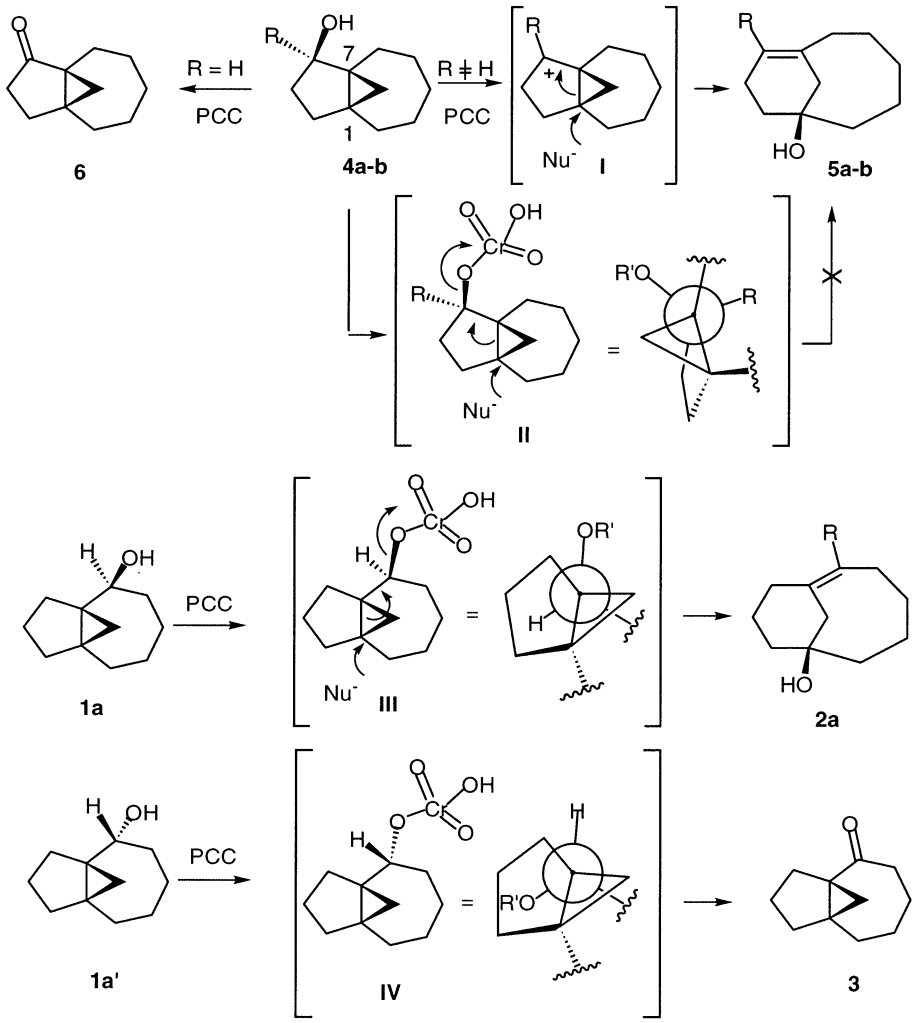


4a, R = H
4b, R = Me

5a, R = H
5b, R = Me

6

Starting material	PCC			10% HCl		
	T (°C), *t* (h)	**5** (Yield (%))	**6** (Yield (%))	*T* (°C), *t* (h)	**5** (Yield (%))	**6** (Yield (%))
4a	rt, 0.8	0	80	60, 10	92	0
4b	rt, 0.8	83	0	rt, 3	90	0



Scheme 4. Mechanism of the rearrangement induced by PCC and Newman projections according to the C7–C8 bond of the tricyclo[5.3.1.0]undecane system.

pound can be oxidized or rearranged by a stepwise ionic mechanism (Scheme 4).

We have demonstrated that tricyclo[5.3.1.0]undecanols can be transformed to bicyclo[5.3.1.0]undecanols in good yields under mild conditions by using PCC. The use of other PCC-induced rearrangements in the synthesis of natural products is under investigation.

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12. The ratio was determined by GC/MS at 70 eV by using a Hewlett Packard 5971 instrument.
13. Ketone **12** was obtained by oxidation of **1a**/**1a**′ by using PDC (3 equiv.) in CH_2Cl_2.
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17. Compound **4a**;[9b] IR (film): 3580 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10 (d, 1H, $J=4.8$ Hz); 0.58 (d, 1H, $J=4.8$ Hz); 0.80–2.00 (m, 15H), 4.08 (t, 1H, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.7 (t), 26.5 (t), 26.6 (t), 29.7 (t), 29.9 (t), 31.4 (t), 32.0 (t), 32.6 (t), 36.8 (s), 77.0 (d); MS (EI, 70 eV) m/z: 166 (28), 151 (24), 148 (12), 137 (59), 123 (100), 109 (51), 91 (47), 81 (55), 55 (34).
18. To a solution of tricyclo[5.3.1.0]undecanols (0.2 g, 1.2 mmol), dissolved in CH_2Cl_2 (3 mL), was added PCC (0.77 g, 3.6 mmol) at 25°C. After completion of the reaction (indicated by TLC and GC/MS) the reaction mixture was diluted with ether and filtered on Celite. The organic phase was concentrated in vacuo and the residue was purified by silica gel chromatography (hexanes/EtOAc: 9/1).
19. To a solution of tricyclo[5.3.1.0]undecanols (0.2 g, 1.2 mmol), dissolved in THF (2 mL), was added HCl (10% in H_2O) (2 mL) at 25°C. After completion of the reaction (indicated by TLC and GC/MS), the reaction mixture was extracted with ether. The organic phase was washed with H_2O and then with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/EtOAc: 9/1).
20. Compound **2a**; IR (film): 3340 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09–3.10 (m, 16H), 5.50 (d, 1H, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9 (t), 26.2 (t), 27.5 (t), 32.2 (t), 34.9 (t), 37.0 (t), 40.1 (t), 40.3 (t), 77.8 (s), 122.4 (d), 139.9 (s); MS (EI, 70 eV) m/z: 166 (5), 151 (35), 148 (91), 133 (40), 123 (87), 106 (61), 97 (100).
21. The relative stereochemistry of the tertiary alcohol in **2a** was proved by hydrogenation to the saturated alcohol described in the literature: Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.
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