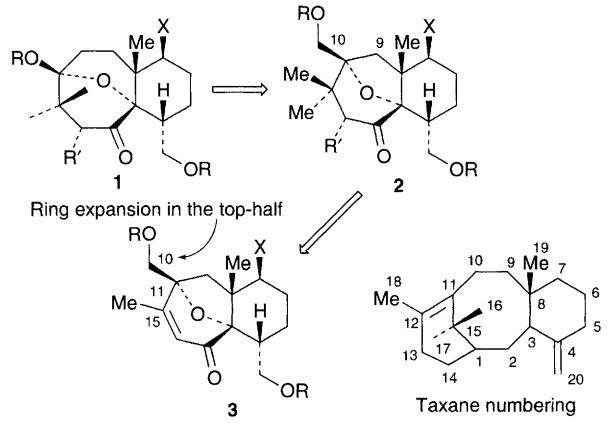
New Strategy for the Synthesis of the Taxane Diterpenes: Formation of the Eight-membered *B*-ring of Taxol by Semi-pinacol Rearrangement

Philip Magnus,* Louis Diorazio, Timothy Donohoe, Melvyn Giles, Philip Pye, James Tarrant and Stephen Thom

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

Solvolysis of the neopentyl triflates **14**, **25** and **32** resulted in ring expansion of a seven-membered ring into the eight-membered ring required for the synthesis of the taxanes diterpenoids,

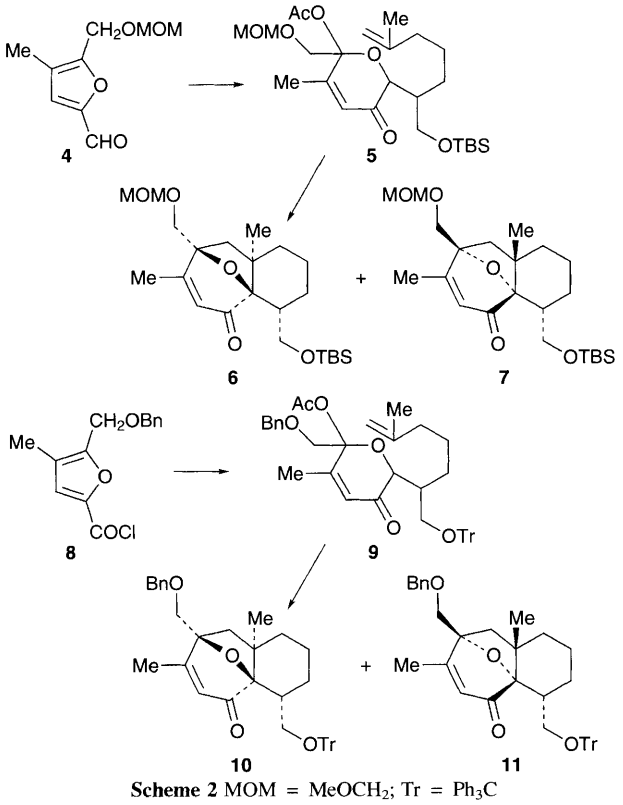
Our previous papers have focused on the reductive cleavage of an internal cyclopropane bond (C-1/C-11) to construct the eight-membered *B*-ring of the taxanes.[1] An alternative approach that still utilizes the bicyclo[5.4.0]undecenones **3** (X = OTBS and X = H) is shown in Scheme 1. Conjugate addition of a methyl group to **3** leads to **2**, which upon suitable activation of the C-10 alcohol and ionization (solvolysis), has the potential to undergo a semi-pinacol-type rearrangement to give **1**.[2] In this paper we report the implementation of this strategy.



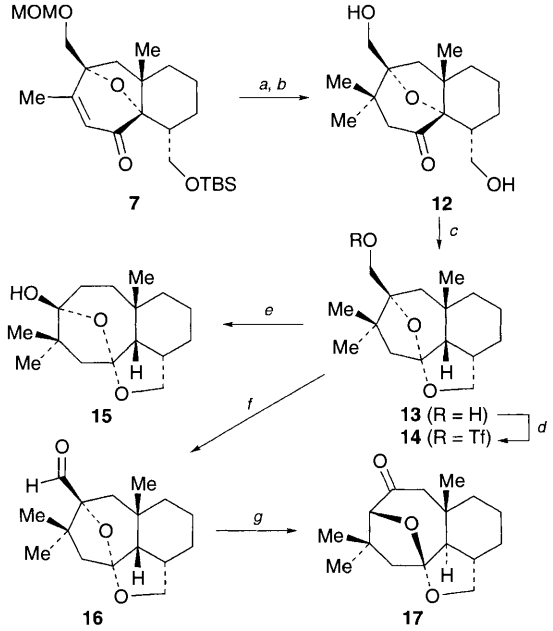
Scheme 1 Ring expansion strategy (X = OTBS or H); TBS = Bu^tMe_2Si

Using the same set of transformations we developed for the unsubstituted bicyclo[5.4.0]undecenones,[1] we have converted the furan-carboaldehyde **4** into the pyrylium ylide precursor **5**. Heating **5** in toluene in the presence of DBU gave a mixture of **6** and **7** (70%, 1 : 8 ratio). Similarly, we have converted the furan acid chloride **8** *via* **9** (chiral), into **10** and **11** (45% over three steps, 1 : 11 ratio), Scheme 2. Treatment of **7** with MeMgBr–CuBr–Me_2S, followed by exposure to TsOH–MeOH gave the diol **12**. Reductive cleavage (Hg–Zn amalgam) of the oxido-bridge under acidic conditions resulted in internal ketalization to give **13** (structure by X-ray crystallography†). Treatment of the derived triflate **14** with CF_3CH_2OH–H_3O^+ resulted in a rapid and clean conversion into the spiro-hemiketal **15** (100%; structure by X-ray crystallography†). Oxidation of **13** gave the aldehyde **16**, which upon treatment with BF_3·OEt_2 resulted in ring expansion and α-ketol shift (acyloin rearrangement) to give the ketone **17** (structure by X-ray crystallography†). It is interesting to note that the *B*/*C* ring fusion in **15** is *cis*-fused, whereas the ring fusion in **17** is *trans*-fused, Scheme 3.

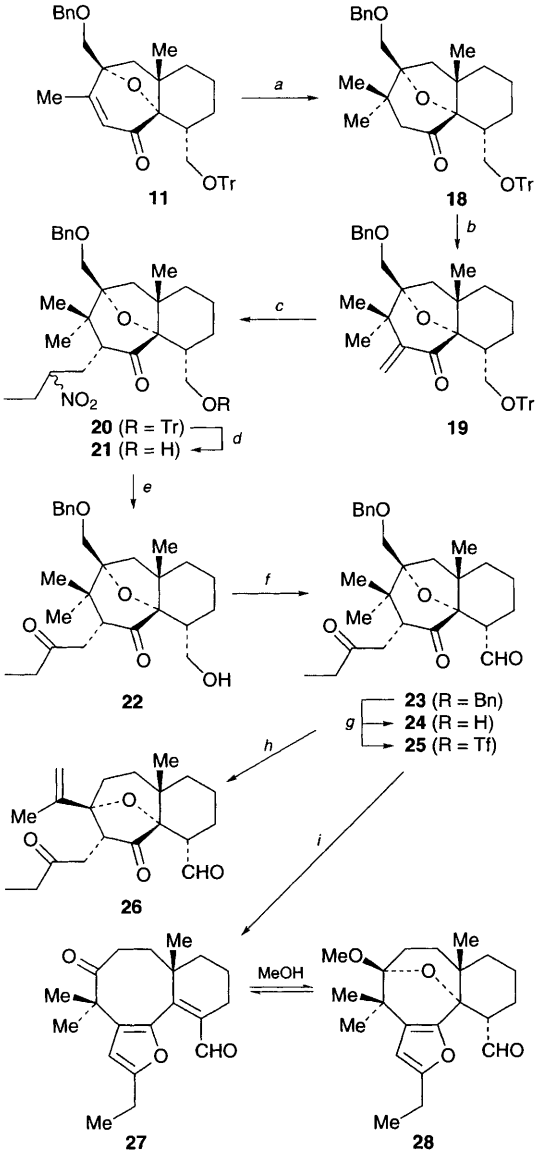
The semi-pinacol ring expansion strategy can be used where the oxido-bridge is β-eliminated rather than reductively opened. Treatment of **18** with potassium hexamethyldisilazide (KHMDS) in tetrahydrofuran followed by paraformaldehyde resulted in the exomethylene enone **19** (95%). The exomethylene ketone **19** was exposed to 1-nitropropane–Me_2SO–K_2CO_3 to give the conjugate addition adduct **20** (>90%). The nitro group was transformed into a ketone by the titanium trichloride modification of the Nef reaction, and the C-20 trityl group removed to give **22**. Dess–Martin oxidation of **22** gave **23**.



Scheme 2 MOM = $MeOCH_2$; Tr = Ph_3C



Scheme 3 *Regents and conditions*: *a*, MeMgBr–CuBr·SMe_2 (80%); *b*, TsOH–MeOH (76%); c, Zn–Hg–HCl, PhMe (79% yield of **13**); *d*, Tf_2O–2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −10 °C (80%); *e*, CF_3CH_2OH–H_2O–H_2SO_4, 80 °C, 1 h (100%); *f*, $Pr_4N^+RuO_4^-$ (cat.), *N*-methylmorpholine *N*-oxide, room temp. (64%); *g*, BF_3·OEt_2, CH_2Cl_2, 3 days, room temp. (70%)

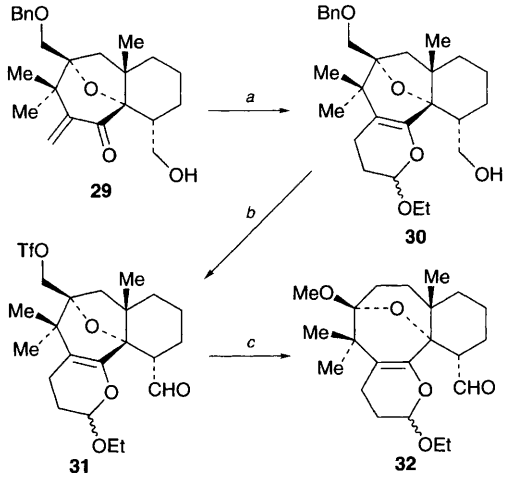


Scheme 4 *Reagents and conditions*: *a*, MeMgBr–CuBr·SMe_2 (95%); *b*, KHMDS–$(CH_2O)_n$, room temp. (95%); *c*, 2-nitropropane–Me_2SO–K_2CO_3, 1 h, room temp. (93%); *d*, TsOH, CH_2Cl_2–MeOH (89%); *e*, $TiCl_3$, MeOH, 12 h, room temp. (75%); *f*, Dess–Martin oxidation (86%); *g*, i, $Pd(OH)_2$, cyclohexene, Pr^iOH (**24**, 97%); ii, Tf_2O-2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −40 °C (used immediately); *h*, Bu^tOH, 2,6-di-*tert*-butyl-4-methylpyridine, reflux (**26**, 65%); *i*, 2,6-lutidine, MeOH, reflux, 20 h (53%)

Hydrogenolysis of the benzyl ether provided **24**, which was converted into the triflate derivative **25** (80% from **20**) (Tf = CF_3SO_2). Solvolysis of **25** in methanol in the presence of lutidine gave the ring-expanded methoxy ketal **28** (structure by X-ray crystallography†). The same series of transformations have been carried out with the 7-hydroxy group present.

Treatment of **28** with lithium diisopropylamide caused β-elimination to give **27**, which readily reforms **28** when exposed to methanol. Under the reaction conditions the 1,4-diketone **25** is rapidly converted into a furan. If the reaction is conducted under more basic conditions (DBU), that prevent furan formation, ring expansion does not take place and a C-10 spiro epoxide was isolated. Curiously, when **25** was treated with Bu^tOH–2,6-di-*tert*-butyl-4-methylpyridine under reflux, the rearranged adduct **26** was isolated (65%), Scheme 4.

While the exomethylene ketone **19** did not react with ethyl vinyl ether under the Danishefsky conditions [$Eu(fod)_3$], the C-20 deprotected compound **29** cleanly gave the dihydropyran **30**



Scheme 5 *Reagents and conditions*: *a*, ethyl vinyl ether, $Eu(fod)_3$ (84%); *b*, i, Dess–Martin oxidation (84%); ii, $Pd(OH)_2$, cyclohexene, Pr^iOH (95%); iii, Tf_2O–2,6-lutidine, CH_2Cl_2, −40 °C (used immediately); *c*, 2,6-lutidine, MeOH (82%)

as a mixture or epimers at the anomeric position.[3] Dess–Martin oxidation of **30**, followed by hydrogenolysis of the benzyl protecting group and treatment with Tf_2O–2,6-lutidine gave the neopentyl triflate **31**. Heating **31** in methanol in the presence of 2,6-lutidine (trific acid scavenger) resulted in ring expansion to give **32** (82%), Scheme 5.

The semipinacol rearrangement approach to the *BC*-rings of the taxanes proceeds in good yields, and illustrates the strategic flexibility of the bicyclo[5.4.0]undecenones **3** (X = OTBS and H).[1]

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Footnote

† *Crystal data*: **13**, $C_{16}H_{26}O_3$, triclinic, space group $P\bar{1}$, T = −90 °C, a = 6.333(3), b = 9.183(3), c = 12.537(6) Å, α = 86.99(3), β = 81.29(4), γ = 83.60(3)°, Z = 2, 3289 unique reflections, 1881 with $F > 4\sigma(F)$; Mo-Kα radiation. R (on F) = 0.052, R_w (on F) = 0.0475.

15, $C_{16}H_{26}O_3$, monoclinic, space group $P2_1/c$, T = −78 °C, a = 9.694(2), b = 13.68(3), c = 11.904(4) Å, β = 113.27(2)°, Z = 4, 3338 unique reflections, 2325 with $F > 4\sigma(F)$, Mo-Kα radiation, R (on F) = 0.044, R_w (on F) = 0.047.

17, $C_{16}H_{24}O_7$, orthorhombic, space group $P2_12_12_1$, T = −90 °C, a = 7.790(12), b = 10.146(3), c = 17.849(5) Å, Z = 4, 1878 unique reflections; Mo-Kα radiation. R (on F) = 0.048, R_w (on F^2) = 0.118.

28, $C_{21}H_{30}O_4$, orthorhombic, space group $P2_12_12_1$, T = −100 °C, a = 7.8007(15), b = 15.213(4), c = 15.792(4) Å, Z = 4, 2519 unique reflections, 2139 with $F > 4\sigma(F)$, Mo-Kα radiation. R (on F) = 0.040, R_w (on F) = 0.045.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1, 1995.

References

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2 D. J. Coveney, 'The Semipinacol and Other Rearrangements', in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and G. Pattenden, Pergamon, Oxford, 1991, vol. 3, p. 777.

3 M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1983, **105**, 3716.