Total Synthesis of Taxol. 4. The Final Stages and Completion of the Synthesis

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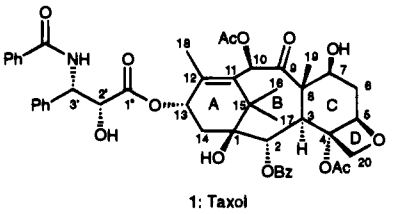
Abstract: The total synthesis of (−)-Taxol has been achieved. Functional group manipulation of diol **2** provided the ABC ring system with the correct C9-keto, C10-acetyloxy functionality. Careful optimization allowed the oxidation of the C5−C6 alkene in **4** at C5 via a hydroboration reaction. Functional group manipulation of this product, **29**, provided, through two routes, the oxetane D ring as **36**. Following the method developed by degradative studies provided the natural enantiomer of Taxol (**1**).

Introduction

With a route to optically active diol **2** secured,[1] a total synthesis of Taxol (**1**, Figure 1) looked quite feasible. However, several issues still remained to be addressed before the final goal could be reached. Amongst them were the functional group adjustments at C9 and C10, the installment of an oxygen at the C5 position, oxetane construction, oxygenation at C13, and side-chain attachment. Below we describe solutions to these problems and, thus, the total synthesis of Taxol (**1**).

Final Stages of the Total Synthesis

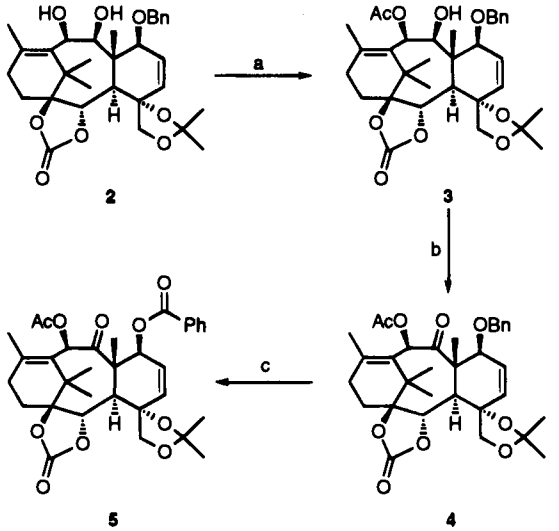
a. Selective Functionalization at C9 and C10. Continuing the sequence from diol **2**[1] (Scheme 1), our strategy toward Taxol (**1**) next called for the adjustment of the functional groups at C9 and C10 to their final form. Arriving at the desired C9-keto, C10-acetate functionality required differentiating between the two hydroxyl groups of diol **2**. Fortunately, the higher reactivity of the allylic C10 hydroxyl group provided high selectivity in the desired direction when compound **2** was exposed to 1.5 equiv of Ac_2O and DMAP in methylene chloride. The resulting monoacetate **3** (Scheme 1, 95% yield) was oxidized cleanly with TPAP−NMO[2] to afford, in 93% yield, the desired 9-keto, 10-acetate **4**. The absence of a conjugated enone in **4** (as observed in the ^{13}C NMR) and the detection of long-range coupling (J < 1.5 Hz) between the C10 proton (δ 5.65, $CDCl_3$, 500 MHz) and the C12 methyl group (δ 1.68) of monoacetate **3** (^1H NMR decoupling experiments) suggested the indicated regiochemistry of these intermediates. This assignment was confirmed by X-ray crystallographic analysis of benzoate **5**, obtained by PCC oxidation[3] of compound **4** (see Scheme 1, and ORTEP drawing in Figure 2). This regioselectivity is in contrast to that observed in the exclusive formation of the 9-camphonate ester described in the preceding paper,[1] in which a speculative explanation for this discrepancy is proposed. It was now time to address the introduction of an alcohol at C5.



1: Taxol

Figure 1. Structure and numbering of Taxol (**1**).

Scheme 1. Functionalization of the C9 and C10 Positions of the Taxoid Framework[a]



[a] Reagents and conditions: (a) 1.5 equiv of Ac_2O, 1.5 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 2 h, 95%; (b) 0.1 equiv of tetrapropylammonium perruthenate (TPAP), 3.0 equiv of 4-methylmorpholine *N*-oxide (NMO), CH_3CN, 25 °C, 2 h, 93%; (c) 30 equiv of pyridinium chlorochromate (PCC), 50 equiv of NaOAc, Celite, benzene, reflux, 1 h, 50%. Bn = CH_2Ph.

b. Early Attempts to Hydroborate the C5−C6 Double Bond. Our experience with the hydroboration of ring C systems[4,5] led us to adopt similar tactics for the real system. Potential differentiation of the two faces of the double bond in

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(1) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645.

(2) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23* (1), 13.

(3) Angyal, S. J.; James, K. *Carbohydr. Res.* **1970**, *12*, 147.

(4) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

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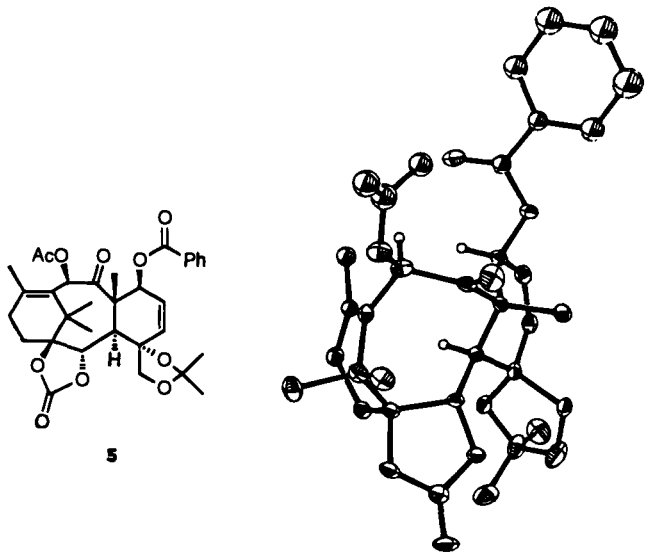


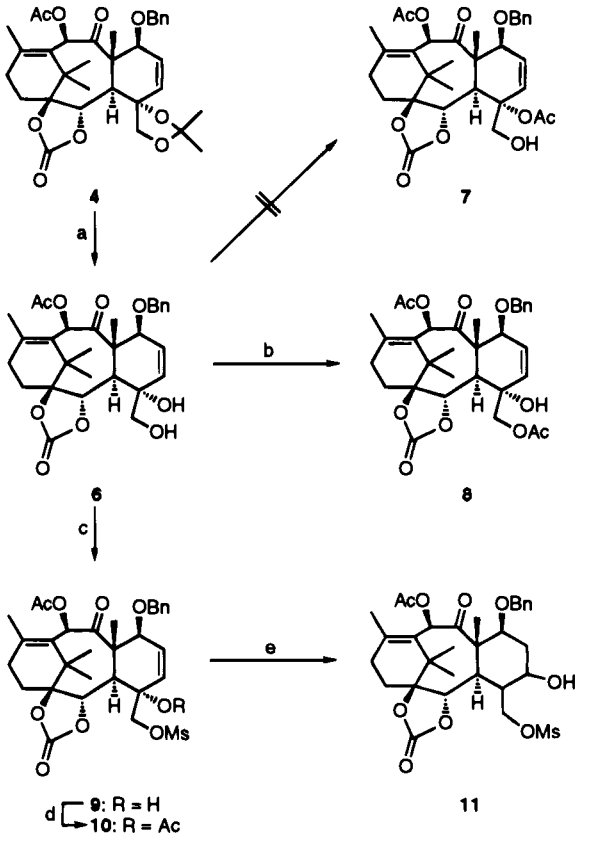
Figure 2. ORTEP diagram for benzoate **5**.

ring C of intermediate **4** by an incoming reagent was not obvious by inspection of molecular models. It was, therefore, decided to initially explore the utilization of the C20 hydroxyl group as a handle to direct hydroboration from the β face of the molecule and at the C5 position as in the simple C ring case. To this end the acetonide group was removed from **4** under acid conditions to afford diol **6** (Scheme 2, 88% yield based on 53% conversion). Attempts to hydroborate[6] **6** under a variety of conditions failed, presumably due to the formation of a stable 5-membered ring borane complex involving the two hydroxyl groups that is both unable to reach the internal alkene and prohibitively bulky for external hydroboration.

We next considered using the 4-acetoxy, 20-hydroxy compound **7** (Scheme 2) as a possible substrate for the desired hydroboration reaction, but unfortunately, all attempts to prepare this intermediate met with failure. Under the various conditions used, the acetate group migrated facilely from the C-4 to the C20 alcohol,[7] leading to either the primary acetate **8** or the starting diol **6** rather than the desired tertiary acetate **7**. It became clear that the acetate at C4 would have to be installed after oxetane formation or in an intermediate in which the C20 hydroxy group would remain blocked until oxetane ring closure. We, therefore, turned to the C4 acetate, C20 mesylate **10**, prepared from diol **6** by sequential mesylation (94% yield) and acetylation (90% yield) as detailed in Scheme 2. Hydroboration of this compound (**10**) with borane in THF, however, resulted not only in hydroxylation at C5 but also in concomitant reductive cleavage of the C4 acetate to afford compound **11** as the major product (67% yield) whose stereochemistry at both the C4 and C5 centers was left unassigned. Similar observations have previously been reported with simple allylic derivatives.[8]

In order to lower the propensity of the C4 substituent toward reductive elimination, the 4-benzyloxy compounds **17** and **19** (Scheme 3) were chosen as the next potential candidates for hydroboration. Exposure to KH and benzyl bromide[9] failed to convert mesylate **9** to the desired benzyl ether **19**, leading instead to the formation of epoxide **12** (Scheme 3). The same

Scheme 2. Hydroboration Studies 1[a]



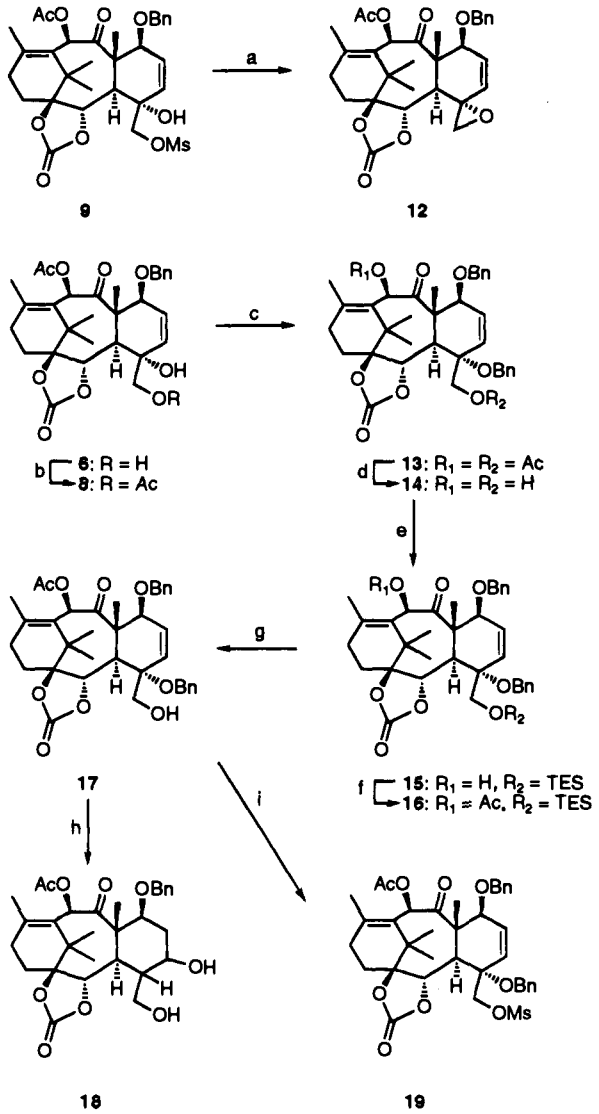
[a] Reagents and conditions: (a) 3.0 equiv of *p*-toluenesulfonic acid, MeOH, 25 °C, 48 h, 88% based on 53% conversion; (b) 5.0 equiv of Dess–Martin periodinane, CH_2Cl_2, 25 °C, 3 h, then 20 equiv of Ac_2O, 25 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 3 h, then 2.0 equiv of n-Bu_4NBH_4, THF, 25 °C, 1 h, 66% from **6**; (c) 1.2 equiv of MsCl, 3.0 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h, 94%; (d) 10 equiv of Ac_2O, 15 equiv of DMAP, CH_2Cl_2, 25 °C, 5 h, 90%; (e) 10 equiv of BH_3·THF, THF, 25 °C, 2 h, then excess H_2O_2, saturated aqueous $NaHCO_3$, 0.5 h, 67%. Bn = CH_2Ph, Ms = SO_2CH_3.

conditions, however, smoothly converted the corresponding acetate **8** (obtained conveniently by monoacetylation of diol **6**) to the C4 benzyloxy derivative **13** (76% yield). Preparation of **17** from **13** required complete deacetylation under basic hydrolysis conditions, followed by selective silylation at C20 (triethylsilyl group), acetylation at C10, and desilylation of the C20 hydroxyl group (52% overall yield). Again, hydroboration of **17** was disappointing: the major product was the C4 deoxy compound **18**. Hydroboration of the C4-benzyloxy, C20-mesylate **19**, obtained through mesylation of **17**, also failed: exhibiting sluggish reactivity and undesirable products.

The unwillingness of the C4-benzyloxy mesylate **19** to enter facilely into hydroboration reactions prompted us to attempt this reaction on the sterically less demanding C4-hydroxy, C20-mesylate **9** (Scheme 4). Thus, exposure of **9** to excess borane in THF followed by oxidative workup resulted in the formation of diol **20** as the major product and in 23% yield. The indicated α stereochemistry of the newly introduced C5 hydroxyl group was based on ^1H NMR data and was confirmed by chemical correlation as outlined in Scheme 4. Thus, treatment of **20** with Et_3N, DMAP, and Ac_2O resulted in acetylation and intramolecular displacement of the mesylate group to give epoxide **21** (75% yield), which was debenzylated by hydrogenolysis, leading to compound **22** (95% yield). The latter compound was identical with a sample prepared from 10-deacetylbaccatin III (**23**) through intermediate **24**[10] by the following short sequence: (a) exposure of **24** to Meerwein's reagent[7] leading to **25** (59%) and **26** (19%); (b) mesylation of the minor product (**26**) to give

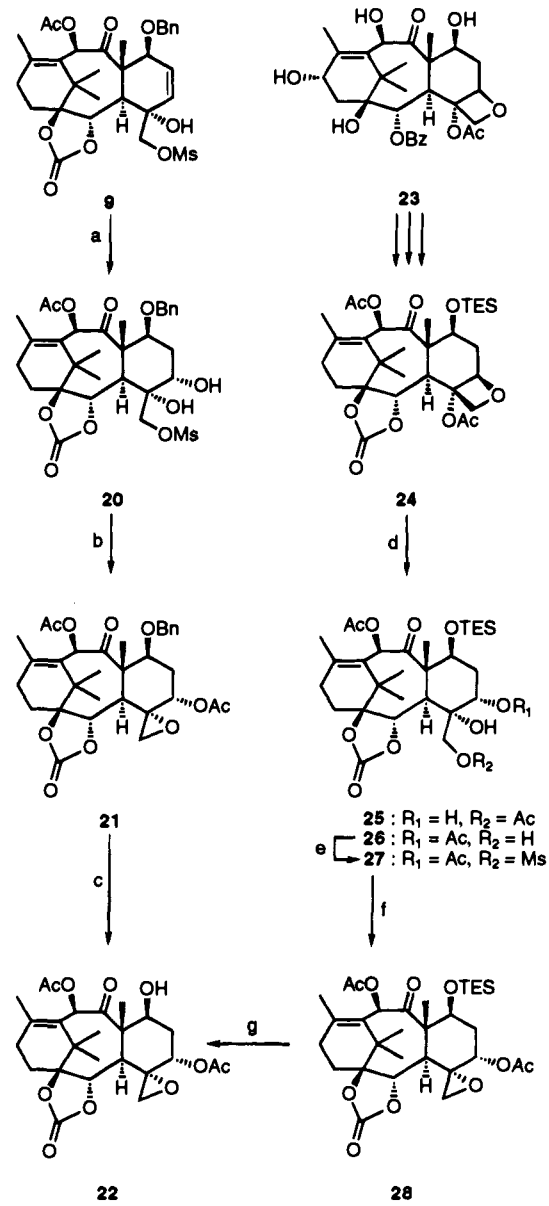
(5) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118.
(6) Smith, K.; Pelter, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8, p 703.
(7) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114.
(8) Brown, H. C.; Knights, E. F. *J. Am. Chem. Soc.* **1968**, *90*, 4439. Pasto, D. J.; Hickman, J. *J. Am. Chem. Soc.* **1968**, *90*, 4445.
(9) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529.

Scheme 3. Hydroboration Studies 2[a]



[a] Reagents and conditions: (a) 1.3 equiv of KH, 5.0 equiv of $PhCH_2Br$, 0.05 equiv of *n*-Bu_4NI, Et_2O, HMPA, 25 °C, 15 min, 79%; (b) 1.2 equiv of Ac_2O, 1.5 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 20 min, 95%; (c) 5.0 equiv of KH, 15 equiv of $PhCH_2Br$, 0.05 equiv of *n*-Bu_4NI, Et_2O, HMPA, 25 °C, 4 h, 76%; (d) 10 equiv of DBU, MeOH, CH_2Cl_2, 25 °C, 3 h, 98%; (e) 1.2 equiv of Et_3SiCl, 1.5 equiv of DMAP, DMF, 25 °C, 1 h; (f) 6.0 equiv of Ac_2O, 6.0 equiv of DMAP, CH_2Cl_2, 25 °C, 0.5 h; (g) HF·pyridine, THF, 25 °C, 1 h, 52% from **14**; (h) 5.0 equiv of BH_3·THF, THF, 0 °C, 0.5 h, 25 °C, 4 h, then excess H_2O_2, aqueous $NaHCO_3$, 0.5 h; (i) 3.0 equiv of MsCl, 5.0 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h, 94%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Bn = CH_2Ph, Ms = SO_2CH_3, TES = $SiEt_3$.

Scheme 4. Chemical Corrolation Studies[a]



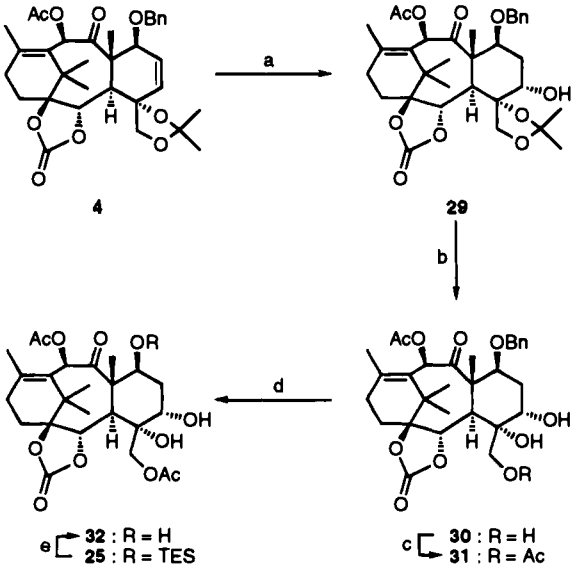
[a] Reagents and conditions: (a) 10 equiv of BH_3·THF, THF, 25 °C, 1.5 h, then excess H_2O_2, aqueous $NaHCO_3$, 0.5 h, 23%; (b) 30 equiv of Ac_2O, excess Et_3N, 0.05 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 12 h, 75%; (c) H_2, $Pd(OH)_2$/C, EtOH, 25 °C, 1 h, 95%; (d) 2.1 equiv of Et_3OBF_4, CH_2Cl_2, 0 °C, 1 h, 59% of **25** plus 19% of **26**; (e) 10 equiv of MsCl, 20 equiv of Et_3N, 2.0 equiv of DMAP, CH_2Cl_2, 25 °C, 0.5 h, 90%; (f) excess KH, THF, 25 °C, 0.5 h, 92%; (g) HF·pyridine, THF, 25 °C, 1 h, 98%. Bn = CH_2Ph, Ms = SO_2CH_3, TES = $SiEt_3$.

27; (c) treatment with KH in THF to form the epoxide ring; and (d) exposure to HF·pyridine to remove the silyl group (81% overall yield from **26**) to afford **22**. This chemical correlation firmly established the regio- and stereoselectivity of the hydroboration reaction of **9**. A better candidate was, however, needed to serve as a precursor to the desired oxetane system.

c. Final Hydroboration Route to a C5α-Hydroxy Intermediate. Having realized that the C5α-hydroxy compounds might be a more accessible series of precursors to the oxetane system, we decided at this point to examine the hydroboration of acetonide **4** (Scheme 5). Inspection of molecular models indicated that the α face was somewhat less hindered than the β face, although the absence of a free hydroxy handle in the vicinity of the C5 position raised questions regarding the regiochemical outcome of the intended hydroboration. In the event, exposure of **4** to excess borane in THF followed by the usual oxidative workup furnished a mixture of the C5α-alcohol **29** (42% yield based on 83% conversion) and its C6 regioisomer (22% yield based on 83% conversion) (Scheme 5). While the stereochemistry of the C6 regioisomer remains unassigned, that of the C5 α-isomer was confirmed by conversion to intermediate **32**, previously obtained from 10-deacetylbaccatin III (**23**) via desilylation of intermediate **25** (Schemes 4 and 5). Thus, acid-catalyzed removal of the acetonide group from **29** afforded triol **30** (80% yield based on 88% conversion). Under carefully controlled conditions, acetylation of the primary hydroxyl group

(10) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 624.

Scheme 5. Hydroboration Studies 3. Successful Hydroboration of the C5–C6 Double Bond[a]



[a] Reagents and conditions: (a) 10.0 equiv of BH_3·THF, THF, 0 °C, 3 h, then excess H_2O_2, saturated aqueous $NaHCO_3$, 25 °C, 1 h, 42% plus 22% of C6-OH regioisomer, based on 83% conversion; (b) MeOH: concd HCl (2:1) 25 °C, 5 h, 80% based on 88% conversion; (c) 1.25 equiv of Ac_2O, 5.0 equiv of pyridine, 0.05 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 0.5 h, 95%; (d) H_2, 10% $Pd(OH)_2$/C, EtOAc, 25 °C, 0.5 h, 97%; (e) HF·pyridine, THF, 25 °C, 2 h, 96%. Bn = CH_2Ph, TES = $SiEt_3$.

in **30** proceeded selectively to afford monoacetate **31** (95% yield). Finally, hydrogenolysis of the benzyl group from **31** furnished alcohol **32**, identical to material obtained from desilylation (HF·pyridine, THF, 96% yield) of **25** in all respects including absolute stereochemistry (synthetic: $[\alpha]^{22}_D$ −85.2 (*c* 0.115, $CHCl_3$); degradative: $[\alpha]^{22}_D$ −85.6 (*c* 0.43, $CHCl_3$). With the synthesis of **32**, the road to Taxol (**1**) was now open.

d. Installation of the Oxetane Ring and Completion of the Total Synthesis. The last remaining challenge in the total synthesis of Taxol (**1**), namely the construction of the oxetane ring, was accomplished following two routes which were based on work previously performed by Potier's group[11] on a taxoid skeleton and by Danishefsky's group[12] on a C ring model system. Both sequences utilized intermediate **25** (available from total synthesis by silylation of **32** with TESCl–pyridine (85% yield) or from degradation of 10-deacetylbaccatin III)[10] and proceeded as outlined below.

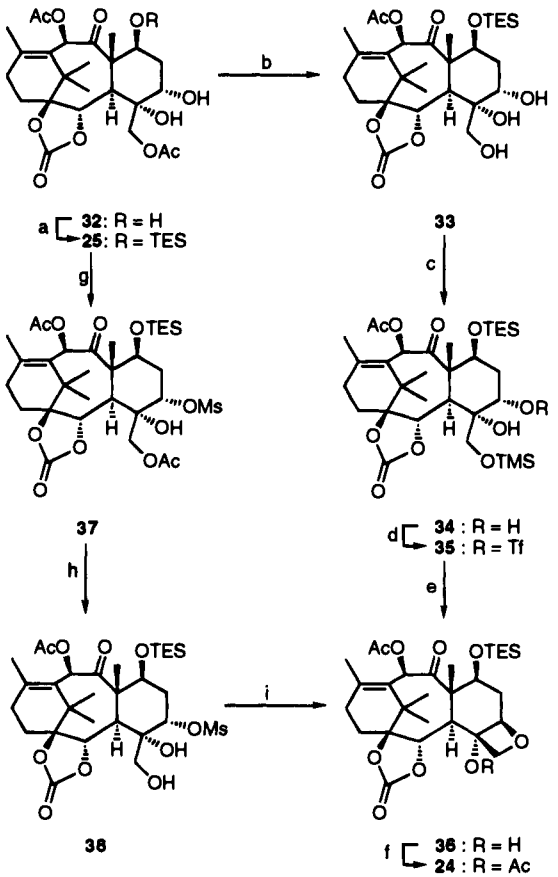
In the first approach, which was modeled after Danishefsky's work,[12] the C20-acetate group was selectively removed from **25** under mildly basic conditions (K_2CO_3–MeOH) to afford triol **33** in 97% yield (Scheme 6). The newly generated primary alcohol was then selectively silylated with TMSCl in the presence of base and exposed to triflic anhydride and base to afford the triflate silyl ether **35** via intermediate **34**. The latter compound converted to oxetane **36** when exposed to mildly acidic conditions (silica gel, CH_2Cl_2) through sequential desilylation of the C20-hydroxyl group followed by internal S_N2 displacement of the triflate. The resulting hydroxy oxetane **36** was acetylated to afford the targeted oxetane system **24** in 40% overall yield from triol **33**.

The second route (Scheme 6), modeled after Potier's studies,[11] featured selective mesylation of diol **25** (73% yield) to furnish hydroxy mesylate **37** which was selectively deacetylated at C20

(11) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.

(12) Magee, T. V.; Bornmann, W. G.; Isaccs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274.

Scheme 6. Construction of the Oxetane Ring[a]



[a] Reagents and conditions: (a) 25 equiv of Et_3SiCl, pyridine, 25 °C, 12 h, 85%; (b) 10 equiv of K_2CO_3, MeOH–H_2O, 0 °C, 15 min, 97%; (c) 10 equiv of Me_3SiCl, 30 equiv of pyridine, CH_2Cl_2, 0 °C, 15 min; (d) 15 equiv of Tf_2O, 30 equiv of *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 0.5 h; (e) 0.05 equiv of camphorsulfonic acid (CSA), MeOH, 25 °C, 15 min, then silica gel, CH_2Cl_2, 25 °C, 1 h, 40% from **33**; (f) 8.0 equiv of Ac_2O, 15 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 4 h, 94%; (g) 10 equiv of MsCl, 20 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h, 73%; (h) 10 equiv of K_2CO_3, MeOH, H_2O, 0 °C, 15 min; (i) 12 equiv of *n*-Bu_4NOAc, butanone, reflux, 5 h, 72% from **37**. TES = $SiEt_3$, TMS = $SiMe_3$, Tf = SO_2CF_3, Ms = SO_2CH_3.

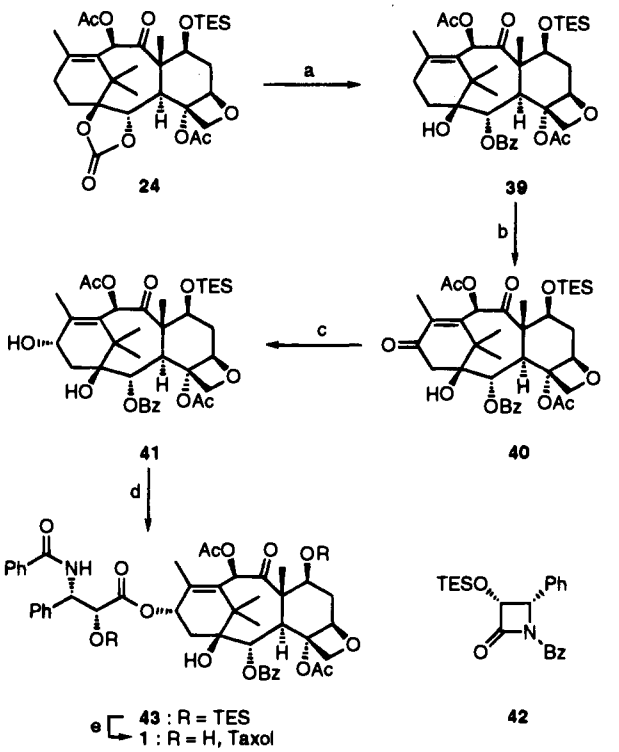
as before, leading to diol **38** in quantitative yield. The latter compound was heated in refluxing butanone to afford hydroxy oxetane **36** (72% yield), which was converted to acetate **24** as described above.

The final drive toward Taxol (**1**) from intermediate **24** was carried out as outlined in Scheme 7 and proceeded along the lines already described in paper 1 of this series.[10] Synthetic Taxol (**1**) was identical with an authentic sample by all usual criteria, including R_f (TLC), t_R (HPLC), $[\alpha]^{22}_D$, IR, ^1H and ^{13}C NMR, HRMS, and biological assay (microtubule stabilization and cytotoxicity against a panel of eight cell lines).

Conclusion

This and the accompanying papers[1,4,10] in this series describe the studies in these laboratories which eventually culminated in the total synthesis of Taxol (**1**). This synthetically challenging molecule with its 11 stereocenters, four skeletal rings, and unusual steric congestion, particularly around its 8-membered ring, provided several serious obstacles and opportunities to create new strategies and to expand the scope and generality of known synthetic methods. New knowledge was gained on issues of regio-, stereo-, and chemoselectivity. Of particular interest were the applications of the Diels–Alder reaction to form rings A and C, the Shapiro and McMurry couplings to

Scheme 7. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) 5.0 equiv of PhLi, THF, −78 °C, 10 min, then 10 equiv of Ac_2O, 5.0 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 2.5 h, 80%; (b) 30 equiv of pyridinium chlorochromate (PCC), 30 equiv of NaOAc, Celite, benzene reflux, 1 h, 75%; (c) excess $NaBH_4$, MeOH, 25 °C, 3 h, 94% based on 88% conversion; (d) 3.0 equiv of $NaN(SiMe_3)_2$, 3.5 equiv of β-lactam **42**, THF, 0 °C, 0.5 h, 86% based on 89% conversion; (e) HF·pyridine, THF, 25 °C, 1.25 h, 80%. TES = $SiEt_3$, Bz = COPh.

construct ring B, and the regioselective opening of carbonates with organometallic reagents to form hydroxy esters.

The resulting convergent route to Taxol (**1**) was utilized for the construction of several new designed taxoids. A number of these compounds obtained by total synthesis[13] or semisynthesis[14,15] have demonstrated interesting properties and shed light on the structural requirements for Taxol's biological activity. Furthermore, water-soluble taxoids that arose from these studies are providing useful information regarding the conformation of Taxol in water[16] and the design of prodrugs[17,18] of this newly established chemotherapeutic agent.

Experimental Section

General Techniques. For a description of general technique, see the first paper in this series.[10] Experimental techniques and data for compounds **5**, **6**, **8**−**22**, **27**, and **28** may be found in the supplementary material.

Acetate 3. A solution of diol **2** (138 mg, 0.0256 mmol) and 4-(dimethylamino)pyridine (DMAP, 47.0 mg, 0.0383 mmol) in CH_2Cl_2 (10 mL) was treated with Ac_2O (0.04 mL, 0.0383 mmol) and stirred at 25 °C for 2 h. After dilution with Et_2O (50 mL), the reaction was quenched with aqueous NH_4Cl (50 mL), and the resulting mixture was stirred at 25 °C for 15 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 30% Et_2O in petroleum ether) to give **3** (141 mg, 95%) as a white foam: R_f = 0.55 (silica, 60% Et_2O in petroleum ether); $[\alpha]^{22}_D$ +181 (*c* 0.48, $CHCl_3$); IR (thin film) ν_{max} 3406, 2385, 1792, 1733, 1654, 1457, 1234, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (band, 5 H, Ar), 5.92 (dd, *J* = 10.0, 2.0 Hz, 1 H, 6-H), 5.62 (d, *J* = 5.0 Hz, 1 H, 10-H), 5.57 (dd, *J* = 10.0, 1.5 Hz, 1 H, 5-H), 5.49 (d, *J* = 4.5 Hz, 1 H, 2-H), 4.69 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.46 (d, *J* = 8.0 Hz, 1 H, 20-H), 4.44 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.28 (b d, *J* = 5.0 Hz, 1 H, 9-H), 3.77 (d, *J* = 8.0 Hz, 1 H, 20-H), 3.71 (b s, 1 H, 7-H), 2.72 (ddd, *J* = 14.5, 10.0, 3.5 Hz, 1 H, 13-H), 2.58 (ddd, *J* = 20.0, 11.5, 3.0 Hz, 1 H, 14-H), 2.42 (b s, 1 H, 9-OH), 2.36 (d, *J* = 4.5 Hz, 1 H, 3-H), 2.09 (s, 3 H, OAc), 2.01 (ddd, *J* = 20.0, 10.0, 3.5 Hz, 1 H, 14-H), 1.80 (ddd, *J* = 14.5, 11.5, 3.0 Hz, 1 H, 13-H), 1.68 (s, 3 H, 18-CH_3), 1.53 (s, 3 H, 19-CH_3), 1.42 (s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$), 1.13 (s, 3 H, 16-CH_3), 1.05 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 153.9, 142.5, 137.4, 135.4, 133.1, 128.5, 128.2, 122.5, 108.2, 93.3, 82.5, 78.1, 75.3, 74.1, 72.5, 71.2, 47.0, 44.7, 39.9, 31.3, 28.9, 27.8, 26.8, 23.6, 21.7, 21.2, 16.2; FAB HRMS (NBA/NaI) *m/e* 605.2720, M + Na^+ calcd for $C_{33}H_{42}O_9$ 605.2727.

Ketone 4. A solution of alcohol **3** (141 mg, 0.242 mmol) in CH_3CN (10 mL) was treated with tetrapropylammonium perruthenate (TPAP, 85.0 mg, 0.0242 mmol) and 4-methylmorpholine *N*-oxide (NMO, 85.0 mg, 0.726 mmol) and stirred at 25 °C for 2 h. After dilution with CH_2Cl_2 (30 mL), the reaction mixture was filtered through silica gel. The resulting solution was concentrated to give **4** (131 mg, 93%) as a white solid: R_f = 0.62 (silica, 30% EtOAc in petroleum ether); $[\alpha]^{22}_D$ +14 (*c* 0.52, $CHCl_3$); IR (thin film) ν_{max} 2925, 1807, 1746, 1717, 1458, 1374, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (band, 5 H, Ar), 6.47 (s, 1 H, 10-H), 5.90 (dd, *J* = 10.5, 2.0 Hz, 1 H, 6-H), 5.67 (dd, *J* = 10.5, 1.5 Hz, 1 H, 5-H), 4.66 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.57 (d, *J* = 11.5 Hz, 1 H, OCH_2Ph), 4.40 (d, *J* = 8.5 Hz, 1 H, 20-H), 4.32 (m, 1 H, 7-H), 4.18 (d, *J* = 5.5 Hz, 1 H, 2-H), 3.78 (d, *J* = 8.5 Hz, 1 H, 20-H), 2.78 (d, *J* = 5.5 Hz, 1 H, 3-H), 2.78−2.70 (band, 2 H, 13-H and 14-H), 2.23 (m, 1 H, 14-H), 2.22 (s, 3 H, OAc), 1.93 (m, 1 H, 13-H), 1.90 (s, 3 H, 18-CH_3), 1.44 (s, 3 H, $C(CH_3)_2$), 1.43 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, 19-CH_3), 1.27 (s, 3 H, 16-CH_3), 1.15 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 169.3, 152.6, 143.3, 137.1, 134.8, 128.9, 128.4, 128.3, 127.9, 123.9, 108.9, 96.5, 81.8, 80.2, 76.5, 76.2, 71.7, 71.1, 58.9, 47.5, 40.5, 29.9, 28.7, 26.8, 26.1, 23.2, 21.8, 20.8, 18.9, 12.8; FAB HRMS (NBA/CsI) *m/e* 713.1720, M + Cs^+ calcd for $C_{33}H_{40}O_9$ 713.1727.

Acetate 25. Conversion of Oxetane 24 to Acetates 25 and 26. A solution of oxetane **24** (14.0 mg, 0.023 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was treated with Et_3OBF_4 (Meerwein's reagent, 1.0 M in CH_2Cl_2, 0.048 mL, 0.048 mmol) and stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (10 mL), washed with aqueous NH_4Cl (5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 50% EtOAc in petroleum ether) to give acetate **25** (8.5 mg, 59%) and acetate **26** (2.8 mg, 19%), both as colorless films.

Acetate 25: R_f = 0.28 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −74 (*c* 0.75, $CHCl_3$); IR (thin film) ν_{max} 3483, 2943, 2884, 1802, 1743, 1461, 1373, 1232, 1120, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1 H, 10-H), 4.46 (d, *J* = 12.0 Hz, 1 H, 20-H), 4.40 (d, *J* = 12.0 Hz, 1 H, 20-H), 4.39 (dd, *J* = 11.0, 3.5 Hz, 1 H, 7-H), 4.23 (d, *J* = 5.0 Hz, 1 H, 2-H), 3.71 (t, *J* = 3.5 Hz, 1 H, 5-H), 3.39 (d, *J* = 5.0 Hz, 1 H, 3-H), 3.16 (s, 1 H, 4-OH), 2.82 (ddd, *J* = 14.0, 10.0, 3.0 Hz, 1 H, 13-H), 2.79 (s, 1 H, 5-OH), 2.71 (m, 1 H, 14-H), 2.25−2.05 (band, 2 H, 6-H and 14-H), 2.14 (s, 3 H, OAc), 2.10 (s, 3 H, 18-CH_3), 1.88 (m, 1 H, 14-H), 1.75 (m, 1 H, 6-H), 1.20 (s, 3 H, 16-CH_3), 1.18 (s, 3 H, 17-CH_3), 1.14 (s, 3 H, 19-CH_3), 0.63 (t, *J* = 7.5 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.58−0.45 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 170.6, 169.2, 153.2, 144.7, 130.1, 93.4, 81.5, 76.0, 74.8, 70.4, 68.5, 64.8, 61.3, 43.0, 40.4, 33.8, 30.2, 26.5, 23.0, 21.1, 20.9, 20.8, 18.9, 11.9, 6.7, 5.1; FAB HRMS (NBA/NaI) *m/e* 647.2845, M + Na^+ calcd for $C_{31}H_{48}O_{11}Si$ 647.2864.

Acetate 26: R_f = 0.36 (silica, 50% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (s, 1 H, 10-H), 5.21 (t, *J* = 3.0 Hz, 1 H, 5-H), 4.30 (dd, *J* = 11.0, 4.5 Hz, 1 H, 7-H), 4.20 (d, *J* = 4.5 Hz,

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1 H, 2-H), 4.03 (d, J = 11.0 Hz, 1 H, 20-H), 3.58 (d, J = 11.0 Hz, 1 H, 20-H), 3.34 (s, 1 H, 4-OH), 3.20 (d, J = 4.5 Hz, 1 H, 3-H), 2.94 (ddd, J = 14.0, 10.0, 3.5 Hz, 1 H, 13-H), 2.75 (m, 1 H, 14-H), 2.20 (s, 3 H, 18-CH_3), 2.18 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.12 (m, 1 H, 14-H), 1.96 (ddd, J = 15.0, 4.5, 4.5 Hz, 1 H, 6-H), 1.90–1.84 (band, 2 H, 6-H and 13-H), 1.19 (s, 3 H, 16-CH_3), 1.14 (s, 3 H, 17-CH_3), 1.04 (s, 3 H, 19-CH_3), 0.86 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.55–0.49 (band, 6 H, $Si(CH_2CH_3)_3$).

Silylation of Triol 32 to 25. A solution of triol **32** (2.0 mg, 0.0039 mmol) in pyridine (0.5 mL) was treated with chlorotriethylsilane (TESCl, 0.017 mL, 0.098 mmol) and stirred at 25 °C for 12 h. The reaction mixture was diluted with Et_2O (10 mL), washed with aqueous $CuSO_4$ (3 × 5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 50% EtOAc in petroleum ether) to give silyl ether **25** (2.0 mg, 85%) as a colorless film.

Alcohol 29. To a solution of acetate **4** (18.7 mg, 0.032 mmol) in THF (2 mL) at 0 °C was added BH_3·THF (1.0 M, 0.32 mL, 0.32 mmol), and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with aqueous $NaHCO_3$ (0.5 mL) and H_2O_2 (0.5 mL), and the resulting solution was allowed to warm to 25 °C, stirred at 25 °C for 1 h, and extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 10% Et_2O in CH_2Cl_2) to give acetate **4** (3.1 mg, 17%), the monoalcohol **29** (6.8 mg, 42% based on 83% conversion) as an amorphous solid, and the corresponding 6-OH regioisomer (3.3 mg, 22% based on 83% conversion) as an amorphous solid.

Alcohol 29: R_f = 0.80 (silica, 10% Et_2O in CH_2Cl_2); $[\alpha]^{22}_D$ −58 (c 0.45, $CHCl_3$); IR (thin film) ν_{max} 3523, 2924, 1803, 1746, 1716, 1459, 1372, 1230, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.22 (band, 5 H, Ar), 6.50 (s, 1 H, 10-H), 5.58 (d, J = 11.5 Hz, 1 H, OCH_2-Ph), 4.48 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.23 (d, J = 8.5 Hz, 1 H, 20-H), 4.16 (d, J = 4.0 Hz, 1 H, 2-H), 4.06 (dd, J = 11.0, 4.5 Hz, 1 H, 7-H), 3.87 (t, J = 3.0 Hz, 1 H, 5-H), 3.77 (d, J = 8.5 Hz, 1 H, 20-H), 3.46 (d, J = 4.0 Hz, 1 H, 3-H), 2.81–2.68 (band, 2 H, 13-H and 14-H), 2.61 (b s, 1 H, 5-OH), 2.36 (m, 1 H, 14-H), 2.20 (m, 1 H, 13-H), 2.19 (s, 3 H, OAc), 2.03 (s, 3 H, 18-CH_3), 1.92 (m, 1 H, 6-H), 1.61 (m, 1 H, 6-H), 1.45 (s, 6 H, $C(CH_3)_2$), 1.22 (s, 3 H, 16-CH_3), 1.18 (s, 3 H, 17-CH_3), 1.13 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 169.2, 153.0, 144.6, 137.5, 129.8, 128.2, 127.9, 127.5, 108.8, 92.7, 84.6, 80.7, 76.1, 73.8, 71.2, 70.5, 68.8, 60.3, 40.6, 30.2, 29.7, 29.7, 29.6, 26.4, 26.2, 23.0, 21.3, 20.9, 18.8, 11.5; FAB HRMS (NBA/NaI) m/e 621.2658, M + Na^+ calcd for $C_{33}H_{42}O_{10}$ 647.2676.

Triol 30. A solution of alcohol **29** (6.8 mg, 0.0114 mmol) in MeOH (2 mL) was treated with concentrated HCl (1 mL) and stirred at 25 °C for 5 h. The reaction was quenched with aqueous $NaHCO_3$ (1 mL), and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with H_2O (2 mL) and brine (2 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 75% EtOAc in petroleum ether) to give monoalcohol **29** (0.8 mg, 12%) and triol **30** (6.8 mg, 80% based on 88% conversion) as an amorphous solid: R_f = 0.30 (silica, 75% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −71 (c 0.16, $CHCl_3$); IR (thin film) ν_{max} 3453, 2906, 1795, 1743, 1714, 1458, 1372, 1233, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.26 (band, 5 H, Ar), 6.49 (s, 1 H, 10-H), 4.55 (d, J = 11.0 Hz, 1 H, OCH_2Ph), 4.45 (d, J = 11.0 Hz, 1 H, OCH_2Ph), 4.20 (d, J = 4.5 Hz, 1 H, 2-H), 4.05 (dd, J = 11.0, 4.5 Hz, 1 H, 7-H), 4.03 (b dd, J = 11.0, 4.5 Hz, 1 H, 20-H), 3.87 (s, 1 H, 4-OH), 3.73 (b t, J = 2.5 Hz, 1 H, 5-H), 3.52 (b dd, J = 11.0, 3.0 Hz, 1 H, 20-H), 3.35 (d, J = 4.5 Hz, 1 H, 3-H), 3.01 (b s, 1 H, 5-OH), 2.92 (ddd, J = 14.5, 10.5, 4.0 Hz, 1 H, 13-H), 2.72 (ddd, J = 20.0, 12.0, 4.0 Hz, 1 H, 14-H), 2.59 (m, 1 H, 20-OH), 2.30 (ddd, J = 14.5, 3.5, 3.0 Hz, 1 H, 6-H), 2.21 (ddd, J = 20.0, 10.5, 3.0 Hz, 1 H, 14-H), 2.17 (s, 3 H, OAc), 2.03 (s, 3 H, 18-CH_3), 1.87 (ddd, J = 14.5, 12.0, 2.5 Hz, 1 H, 13-H), 1.61 (m, 1 H, 6-H), 1.20 (s, 3 H, 19-CH_3), 1.16 (s, 3 H, 16-CH_3), 1.15 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 169.2, 153.4, 144.7, 137.7, 129.8, 128.2, 127.8, 127.5, 97.9, 93.4, 81.5, 76.1, 74.5, 73.7, 72.5, 62.5, 60.0, 42.8, 30.2, 29.6, 29.4, 26.3, 22.8, 21.3, 20.9, 18.8, 12.4; FAB HRMS (NBA/NaI) m/e 581.2341, M + Na^+ calcd for $C_{30}H_{38}O_{10}$ 581.2363.

Acetate 31. A solution of triol **30** (4.5 mg, 0.008 mmol) in CH_2Cl_2 (1 mL) was treated with Ac_2O (0.0009 mL, 0.010 mmol), pyridine (0.003 mL, 0.040 mmol), and 4-(dimethylamino)pyridine (DMAP, catalytic) and stirred at 25 °C for 0.5 h. The reaction was quenched with aqueous $NaHCO_3$ (1 mL), and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 50% EtOAc in petroleum ether) to give diol **8** (4.6 mg, 95%) as an amorphous solid: R_f = 0.40 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −51 (c 0.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (band, 5 H, Ar), 6.51 (s, 1 H, 10-H), 4.55 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.48 (d, J = 12.0 Hz, 1 H, 20-H), 4.44 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.41 (d, J = 12.0 Hz, 1 H, 20-H), 4.22 (d, J = 4.5 Hz, 1 H, 2-H), 4.06 (dd, J = 11.0, 4.5 Hz, 1 H, 7-H), 3.74 (m, 1 H, 5-H), 3.41 (d, J = 4.5 Hz, 1 H, 3-H), 3.14 (s, 1 H, 4-OH), 2.83 (ddd, J = 14.5, 10.5, 4.0 Hz, 1 H, 13-H), 2.75 (b s, 1 H, 5-OH), 2.72 (m, 1 H, 14-H), 2.29 (ddd, J = 14.5, 4.0, 4.0 Hz, 1 H, 6-H), 2.18 (m, 1 H, 14-H), 2.17 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.03 (s, 3 H, 18-CH_3), 1.90 (m, 1 H, 13-H), 1.69 (m, 1 H, 6-H), 1.28 (s, 3 H, 19-CH_3), 1.20 (s, 3 H, 16-CH_3), 1.15 (s, 3 H, 17-CH_3); FAB HRMS (NBA/CsI) m/e 733.1633, M + Cs^+ calcd for $C_{32}H_{40}O_{11}$ 733.1625.

Triol 32. Hydrogenation of 31. A solution of diol **31** (4.6 mg, 0.0077 mmol) in EtOAc (1 mL) was treated with $Pd(OH)_2$/C (1.0 mg) under an atmospheric pressure of hydrogen and stirred at 25 °C for 0.5 h. The reaction mixture was filtered, concentrated, and purified by preparative TLC (silica, EtOAc) to give triol **32** (3.8 mg, 97%) as an amorphous solid: R_f = 0.20 (silica, Et_2O); $[\alpha]^{22}_D$ −85.2 (c 0.115, $CHCl_3$); IR (thin film) ν_{max} 3492, 2941, 1795, 1737, 1714, 1457, 1370, 1230, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1 H, 10-H), 4.43 (s, 2 H, 20-CH_2), 4.42 (m, 1 H, 7-H), 4.20 (d, J = 5.0 Hz, 1 H, 2-H), 3.77 (t, J = 3.0 Hz, 1 H, 5-H), 3.39 (d, J = 5.0 Hz, 1 H, 3-H), 3.21 (s, 1 H, 4-OH), 2.83 (s, 1 H, 5-OH), 2.86–2.71 (band, 2 H, 13-H and 14-H), 2.27–2.12 (band, 2 H, 6-H and 14-H), 2.18 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.08 (s, 3 H, 18-CH_3), 1.91 (m, 1 H, 13-H), 1.80 (m, 1 H, 6-H), 1.23 (s, 6 H, 16-CH_3 and 17-CH_3), 1.10 (s, 3 H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 170.8, 170.7, 153.1, 146.7, 129.2, 93.3, 81.6, 76.2, 74.8, 70.2, 68.4, 64.8, 61.1, 42.8, 40.4, 32.4, 30.4, 26.4, 22.9, 21.7, 20.9, 20.8, 18.8, 11.4; FAB HRMS (NBA/CsI) m/e 643.1175, M + Cs^+ calcd for $C_{25}H_{34}O_{11}$ 643.1155.

Desilylation of 25. A solution of diol **25** (6.5 mg, 0.010 mmol) in THF (2.0 mL) at 25 °C was treated with HF·pyridine (0.4 mL) and stirred for 2 h. The reaction mixture was diluted with EtOAc (10 mL), washed with 10% aqueous NaOH (5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, EtOAc) to give triol **32** (5.1 mg, 96%) as a colorless film.

Triol 33. A solution of acetate **25** (96.0 mg, 0.154 mmol) in MeOH (16 mL) at 0 °C was treated with a solution of K_2CO_3 (212 mg, 1.54 mmol) in H_2O (4 mL). The reaction mixture was stirred at 0 °C for 15 min, and the reaction was quenched with aqueous NH_4Cl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give triol **33** (87.0 mg, 97%) as a white foam: R_f = 0.42 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −78 (c 0.25, $CHCl_3$); IR (thin film) ν_{max} 3458, 2955, 1796, 1751, 1714, 1461, 1373, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (s, 1 H, 10-H), 4.39 (dd, J = 11.0, 4.5 Hz, 1 H, 7-H), 4.22 (d, J = 5.0 Hz, 1 H, 2-H), 4.01 (b d, J = 9.5 Hz, 1 H, 20-H), 3.81 (s, 1 H, 4-OH), 3.70 (b s, 1 H, 5-H), 3.52 (d, J = 9.5 Hz, 1 H, 20-H), 3.33 (d, J = 5.0 Hz, 1 H, 3-H), 3.06 (s, 1 H, 20-OH), 2.95–2.85 (band, 2 H, 13-H and 5-OH), 2.71 (m, 1 H, 14-H), 2.23 (ddd, J = 19.5, 9.0, 3.0 Hz, 1 H, 14-H), 2.14 (s, 6 H, OAc and 18-CH_3), 2.12 (m, 1 H, 6-H), 1.86 (ddd, J = 14.0, 12.0, 3.0 Hz, 1 H, 6-H), 1.69 (m, 1 H, 13-H), 1.18 (s, 3 H, 16-CH_3), 1.14 (s, 3 H, 17-CH_3), 1.09 (s, 3 H, 19-CH_3), 0.87 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.60–0.45 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 169.2, 153.9, 144.8, 130.2, 93.7, 81.9, 76.1, 73.6, 71.7, 68.5, 62.6, 61.4, 42.7, 40.5, 33.7, 30.3, 26.4, 22.9, 21.2, 20.9, 18.9, 11.9, 6.7, 5.1; FAB HRMS (NBA/NaI) m/e 605.2735, M + Na^+ calcd for $C_{29}H_{46}O_{10}Si$ 605.2758.

Oxetane 36. Conversion of Triol 33 to 36. A solution of triol **33** (10.0 mg, 0.017 mmol) and pyridine (0.142 mL, 0.51 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was treated with chlorotrimethylsilane (TMSCl, 0.022 mL, 0.17 mmol) and stirred at 0 °C for 15 min. The reaction

was quenched with aqueous $NaHCO_3$ (2.0 mL). The resulting mixture was allowed to warm to 25 °C and extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give the crude silyl ether **34**, which was taken to the next step without further purification.

A solution of silyl ether **34** and *i*-Pr_2EtN (0.090 mL, 0.51 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was treated with triflic anhydride (Tf_2O, 0.044 mL, 0.26 mmol) and stirred at 0 °C for 0.5 h. The reaction was then quenched with aqueous $NaHCO_3$ (1.5 mL), and the resulting mixture was allowed to warm to 25 °C and extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give the crude triflate **35**, which was taken to the next step without further purification.

A solution of triflate **35** in MeOH (2.0 mL) was treated with camphorsulfonic acid (CSA, 0.5 mg, 0.002 mmol) and stirred at 25 °C for 15 min. The reaction was quenched with aqueous $NaHCO_3$ (1.5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting residue was dissolved in CH_2Cl_2 (2.0 mL) and treated with silica gel (E. Merck, 0.1 g) at 25 °C for 1 h. The reaction mixture was filtered, concentrated, and purified by preparative TLC (silica, 50% EtOAc in petroleum ether) to give oxetane **36** (3.9 mg, 40% from **33**) as a colorless film: R_f = 0.35 (silica, 33% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −47 (*c* 0.42, $CHCl_3$); IR (thin film) ν_{max} 3462, 2927, 1805, 1747, 1716, 1595, 1460, 1372, 1237 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1 H, 10-H), 4.82 (dd, *J* = 9.5, 2.0 Hz, 1 H, 5-H), 4.66 (d, *J* = 9.0 Hz, 1 H, 20-H), 4.42 (d, *J* = 9.0 Hz, 1 H, 20-H), 4.37 (d, *J* = 5.5 Hz, 1 H, 2-H), 4.12 (dd, *J* = 10.5, 7.0 Hz, 1 H, 7-H), 2.71 (m, 1 H, 14-H), 2.63 (d, *J* = 5.5 Hz, 1 H, 3-H), 2.62 (m, 1 H, 13-H), 2.48 (ddd, *J* = 15.0, 9.5, 7.0 Hz, 1 H, 6-H), 2.43 (s, 1 H, 4-OH), 2.19 (m, 1 H, 14-H), 2.15 (s, 3 H, OAc), 2.06 (s, 3 H, 18-CH_3), 1.93 (ddd, *J* = 15.0, 10.5, 2.0 Hz, 1 H, 6-H), 1.89 (ddd, *J* = 14.5, 12.0, 2.5 Hz, 1 H, 13-H), 1.62 (s, 3 H, 19-CH_3), 1.19 (s, 3 H, 16-CH_3), 1.18 (s, 3 H, 17-CH_3), 0.87 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.54 (q, *J* = 8.0 Hz, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 169.3, 153.4, 143.9, 131.1, 93.2, 87.5, 80.7, 80.5, 76.5, 73.8, 71.9, 59.7, 51.6, 47.1, 37.8, 30.0, 26.2, 22.9, 21.7, 20.9, 19.0, 9.8, 6.7, 5.1; FAB HRMS (NBA/CsI) *m/e* 697.1790, M + Cs^+ calcd for $C_{29}H_{44}O_9Si$ 697.1809.

Conversion of Mesylate 38 to Oxetane 36. A solution of crude diol **38** (11.0 mg, 0.017 mmol) in butanone (1.0 mL) was treated with *n*-Bu_4NOAc (60.0 mg, 0.20 mmol) and stirred at reflux for 5 h. The reaction mixture was allowed to cool to 25 °C and partitioned between Et_2O (10 mL) and H_2O (5 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 20% EtOAc in petroleum ether) to give oxetane **36** (6.8 mg, 72% from **37**) as a colorless film.

Acetate 24. A solution of oxetane **36** (4.0 mg, 0.0091 mmol) and 4-(dimethylamino)pyridine (DMAP, 17.0 mg, 0.14 mmol) in CH_2Cl_2 (2.0 mL) was treated with acetic anhydride (0.0067 mL, 0.071 mmol) and stirred at 25 °C for 4 h. The reaction mixture was diluted with Et_2O (10 mL), washed with 1 N aqueous HCl (5 mL) and aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 33% EtOAc in petroleum ether) to give acetate **24** (4.0 mg, 94%) as a colorless film: R_f = 0.82 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −49.4 (*c* 0.93, $CHCl_3$); IR (thin film) ν_{max} 2924, 1814, 1728, 1461, 1372, 1238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1 H, 10-H), 4.95 (d, *J* = 9.0 Hz, 1 H, 5-H), 4.60 (A of AB, d, *J* = 9.0 Hz, 1 H, 20-H), 4.47 (B of AB, d, *J* = 9.0 Hz, 1 H, 20-H), 4.43 (dd, *J* = 10.0, 7.5 Hz, 1 H, 7-H), 4.39 (d, *J* = 5.5 Hz, 1 H, 2-H), 3.36 (d, *J* = 5.5 Hz, 1 H, 3-H), 2.71 (m, 1 H, 13-H), 2.56 (m, 1 H, 13-H), 2.17 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.12 (m, 1 H), 2.07 (s, 3 H, 18-CH_3), 1.97 (m, 1 H), 1.88 (m, 2 H), 1.78 (s, 3 H, 19-CH_3), 1.23 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3), 0.88 (t, *J* = 7.5 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.60−0.50 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 170.3, 169.2, 153.1, 144.0, 130.7, 92.8, 84.0, 80.3, 80.0, 76.4, 76.1, 60.3, 43.5, 38.0, 29.7, 29.4, 25.5, 23.1, 21.9, 21.1, 19.1, 9.8, 6.7, 5.2; FAB HRMS (NBA/CsI)*m/e* 739.1929, M + Cs^+ calcd for $C_{31}H_{46}O_{10}Si$ 739.1915.

Mesylate 37. A solution of alcohol **25** (46.0 mg, 0.074 mmol) and 4-(dimethylamino)pyridine (DMAP, 180 mg, 1.48 mmol) in CH_2Cl_2 (6.0 mL) was treated with mesyl chloride (MsCl, 0.056 mL, 0.72 mmol) and stirred at 25 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL), washed with 1 N aqueous HCl (10 mL), aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 20% EtOAc in petroleum ether) to give mesylate **37** (37.0 mg, 73%) as a white solid: R_f = 0.38 (silica, 33% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −40 (*c* 0.50, $CHCl_3$); IR (thin film) ν_{max} 3495, 2925, 1804, 1746, 1461, 1365, 1232 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1 H, 10-H), 4.71 (t, *J* = 2.5 Hz, 1 H, 5-H), 4.53 (d, *J* = 12.0 Hz, 1 H, 20-H), 4.50 (d, *J* = 12.0 Hz, 1 H, 20-H), 4.37 (dd, *J* = 11.0, 4.5 Hz, 1 H, 7-H), 4.26 (d, *J* = 4.5 Hz, 1 H, 2-H), 3.37 (d, *J* = 4.5 Hz, 1 H, 3-H), 3.15 (s, 1 H, 4-OH), 3.08 (s, 3 H, OMs), 2.87 (ddd, *J* = 14.5, 10.0, 3.5 Hz, 1 H, 13-H), 2.74 (ddd, *J* = 19.5, 12.0, 3.5 Hz, 1 H, 14-H), 2.38 (ddd, *J* = 19.5, 10.0, 3.0 Hz, 1 H, 14-H), 2.23 (ddd, *J* = 15.0, 4.5, 2.5 Hz, 1 H, 6-H), 2.19 (s, 3 H, 18-CH_3), 2.18 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.02 (ddd, *J* = 15.0, 11.0, 2.5 Hz, 1 H, 6-H), 1.92 (ddd, *J* = 14.5, 12.0, 3.0 Hz, 1 H, 13-H), 1.27 (s, 3 H, 19-CH_3), 1.22 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3), 0.91 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.59−0.54 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 170.9, 169.2, 152.9, 145.4, 130.0, 81.1, 80.9, 75.9, 73.5, 68.5, 64.4, 61.1, 44.4, 40.4, 38.9, 34.7, 30.0, 29.7, 26.5, 23.1, 21.0, 20.9, 20.7, 18.9, 12.3, 6.7, 5.0; FAB HRMS (NBA/CsI) *m/e* 835.1811, M + Cs^+ calcd for $C_{32}H_{50}O_{13}SiS$ 835.1796.

Diol 38. A solution of acetate **37** (24.0 mg, 0.034 mmol) in MeOH (3.0 mL) at 0 °C was treated with a solution of K_2CO_3 (60.0 mg, 0.34 mmol in 0.5 mL of H_2O) and stirred at 0 °C for 15 min. The reaction was quenched with aqueous NH_4Cl (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$), and concentrated to give crude diol **38**, which was taken to the next step without further purification.

Diol 38: R_f = 0.51 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −35 (*c* 0.63, $CHCl_3$); IR (thin film) ν_{max} 3742, 2925, 1800, 1749, 1716, 1461, 1363, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1 H, 10-H), 4.74 (t, *J* = 3.0 Hz, 1 H, 5-H), 4.38 (dd, *J* = 11.0, 4.0 Hz, 1 H, 7-H), 4.24 (d, *J* = 4.5 Hz, 1 H, 2-H), 4.01 (b d, *J* = 11.0 Hz, 1 H, 20-H), 3.83 (s, 1 H, 4-OH), 3.61 (b d, *J* = 11.0 Hz, 1 H, 20-H), 3.35 (d, *J* = 4.5 Hz, 1 H, 3-H), 3.11 (s, 3 H, OMs), 2.96 (ddd, *J* = 14.5, 10.0, 4.0 Hz, 1 H, 13-H), 2.74 (m, 1 H, 14-H), 2.36 (ddd, *J* = 19.5, 10.0, 3.0 Hz, 1 H, 14-H), 2.26 (ddd, *J* = 15.0, 4.0, 3.0 Hz, 1 H, 6-H), 2.20 (s, 3 H, 18-CH_3), 2.18 (s, 3 H, OAc), 1.98−1.90 (band, 2 H, 6-H and 13-H), 1.22 (s, 3 H, 19-CH_3), 1.17 (s, 3 H, 16-CH_3), 1.16 (s, 3 H, 17-CH_3), 0.90 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.59−0.53 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 169.1, 153.6, 145.4, 130.0, 82.3, 81.3, 76.0, 72.7, 68.4, 62.4, 53.2, 43.8, 40.4, 38.5, 34.6, 30.1, 29.6, 26.4, 22.9, 21.0, 20.8, 18.8, 12.1, 6.6, 4.9; FAB MS (NBA/NaI) *m/e* 683, M + Na^+ calcd for $C_{30}H_{48}O_{12}SiS$ 683.

For the conversion of carbonate **24** to Taxol (**1**) and physical data for compounds **1**, **39**−**41**, and **43**, see the first paper in this series.[10]

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Supplementary Material Available: Experimental techniques and data for compounds **5**, **6**, **8**−**22**, **27**, and **28** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. See any current masthead page for ordering information.

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