for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 5/1) to give **5b** (0.99 g, 97% yield): mp 121.2–121.7 °C; λ_{max} (MeOH) 262 nm (ϵ 10560), λ_{min} (MeOH) 232 nm (ϵ 3810); ^{1}H NMR (Me_2SO-d_6) δ 1.74–2.00 (m, 3 H), 2.20–2.35 (m, 1 H), 3.49–3.55 (m, 1 H), 3.64–3.69 (m, 1 H), 4.00–4.03 (br s, 1 H), 5.03 (s, 1 H), 5.58 (d, 1 H, J = 8.06 Hz), 5.95 (m, 1 H), 7.94 (d, 1 H, J = 8.06 Hz), 11.25 (br s, 1 H); fast atom bombardment mass spectrum, m/z 213 (MH^+). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.95; H, 5.71; N, 13.20.

5′-*O*-Acetyl-2′,3′-dideoxyuridine (5a). The compound **4a** was hydrogenated into **5a** in the same way: mp 80.1–80.6 °C; λ_{max} (MeOH) 262 nm (ϵ 10290), λ_{min} (MeOH) 232 nm (ϵ 3850); ^{1}H NMR (Me_2SO-d_6) δ 1.75–1.87 (m, 1 H), 1.92–2.06 (m, 2 H), 2.05 (s, 3 H), 2.20–2.38 (m, 1 H), 4.14–4.26 (m, 3 H), 5.63 (d, 1 H, J = 8.06 Hz), 5.99 (m, 1 H), 7.66 (d, 1 H, J = 8.06 Hz); fast atom bombardment mass spectrum, m/z 255 (MH^+). Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.02; H, 5.59; N, 10.97.

Acknowledgment. We wish to thank Drs. A. Yamazaki and K. Izawa for their suggestions and Ms. C. Ishijima and Messrs. T. Maita, F. Kakizaki, S. Nishi, and M. Sumikawa for their help in the experiments. Thanks are also due to the staff of the analytical department of this company for spectral measurements and elemental analyses.

General Approach to the Synthesis of Polyquinenes. 9. The Monofunctionalization and Alteration of the Symmetry of the *cis*-Bicyclo[3.3.0]octane-3,7-dione Unit[1]

Kotha Sambasivarao, G. Kubiak, G. Lannoye, and James M. Cook*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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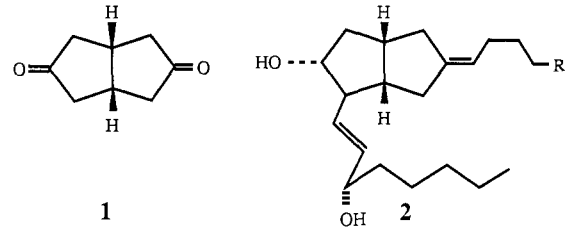
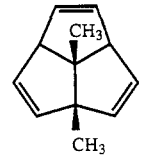
Interest in the synthesis of polyquinanes has gained momentum in recent years due, in part, to the isolation of natural products whose molecular architecture is comprised of polyfused five-membered rings (e.g. capnallane, corriolin, cripnallane).[2] Moreover, interest in the synthesis of nonnatural products such as triquinacene,[3] peristylane,[4] pagodane,[5a] and dodecahedrane[5b] has been stimulated due to the unique topology of such systems,[2] as well as their chemical behavior.[4,5] Retrosynthetic analysis of the molecules mentioned above, via at least one pathway, will ultimately terminate in the structure of a *cis*-bicyclo[3.3.0]octane unit. This versatile building block, represented in the present paper as *cis*-bicyclo[3.3.0]octane-3,7-dione (**1**), is available on large scale from the Weiss reaction.[6,7] Numerous attempts to differentiate between the two five-membered rings of **1** have been reported[8] due to the activity of carboprostacyclines **2**[9] and to the use of **1** in the synthesis of other polyquinanes.[10,11] Previous





3

attempts to monofunctionalize the symmetrical bicyclooctanedione unit **1** have employed multistep synthesis,[2] protection–deprotection sequences accompanied by several recycle passes,[9,12] or alkylation reactions, the yields of which have been only moderate.[13,14] In order to surmount this problem we have recently developed a new approach to the monoalkylation of **1**, which ultimately resulted in the synthesis of centrosubstituted triquinacenes such as **3**.

Initially, a number of obvious methods to monoalkylate **1** were attempted but met with little success.[14] However, the versatility of the Weiss reaction could be exploited at this juncture. When glyoxal **5a** was stirred with di-*tert*-butyl β-ketoglutarate **4b** in alkaline solution, a 93% yield of tetra-*tert*-butyl-3,7-dihydroxy-*cis*-bicyclo[3.3.0]octanetetracarboxylate (**6b**) was realized. This tetraester was converted into the requisite bisenol ether **7b** on stirring with diazomethane (Scheme I). Although various reaction conditions were studied, it was found that monoalkylation of the glyoxal-derived tetra-*tert*-butyl ester **7b** could best be achieved at low temperatures (−30 to −60 °C), as illustrated in Table I. When the temperature rose above this, dialkylation began to compete in the process. Hydrolysis and decarboxylation of the monoalkylated tetraesters represented by **8** gave the corresponding monoalkylated *cis*-bicyclo[3.3.0]octane-3,7-diones **9**. Conditions for this alkylation reaction were developed earlier during

(1) This paper was presented in preliminary form. Lannoye, G.; Rao, K. S.; Cook, J. M. *General Approach to the Synthesis of Polyquinenes via the Weiss Reaction*; presented at the 9th Rocky Mountain Regional American Chemical Society Meeting, Las Vegas, NV, March 27–30, 1988; Abstract 49.

(2) For recent reviews in the area of polyquinanes, see: Paquette, L. A. *Topics in Current Chemistry*; Springer-Verlag, 1984; Vol 119. Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189. Mehta, G. *J. Sci. Ind. Res.* **1978**, *37*, 256. Ramaiah, M. *Synthesis* **1984**, 529. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.

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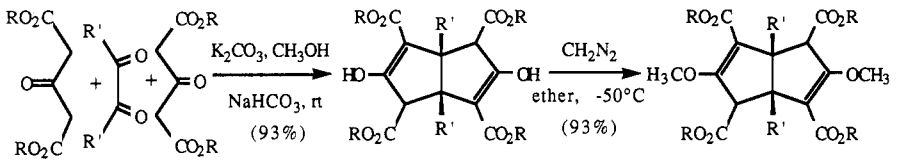
Scheme I



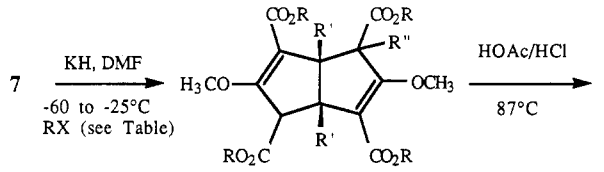
Scheme I

4a, R=Me **5a**, R'=H
4b, R=tBu **5b**, R'=CH_3
5c, R'⌒R'=-$(CH_2)_4$-

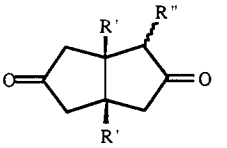
6a, R=Me, R'=H
6b, R=tBu, R'=H
6c, R=tBu, R'=CH_3
6d, R=tBu, R'⌒R'=-$(CH_2)_4$-

7a, R=Me, R'=H
7b, R=tBu, R'=H
7c, R=tBu, R'=CH_3
7d, R=tBu, R'⌒R'=-$(CH_2)_4$-

Scheme II



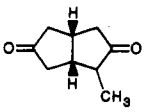
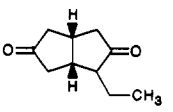
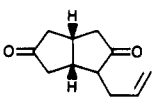
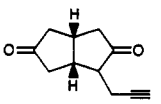
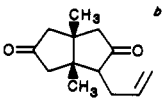
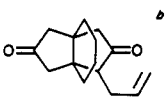
8, R = tBu
R' = alkyl
R" = alkyl



9, R' = alkyl
R" = alkyl

studies on triquinacene.[3b,14] The synthesis of the monomethyl **9a**, monoethyl **9b**, monoallyl **9c**, and monopropargyl **9d** *cis*-bicyclo[3.3.0]octane-3,7-diones was readily achieved via this technology in high yield, as illustrated in Scheme II. Each compound was accompanied by less than 2% of the corresponding dialkylated product. The symmetry of *cis*-bicyclo[3.3.0]octane-3,7-dione (1) has been altered by taking advantage of the bisenol nature of the tetraester **6**, followed by the effect of the *tert*-butyl ester groups on the alkylation step. The large *tert*-butyl ester groups of **6b**, in comparison to the methyl esters in **6a**, retard the rate of addition of electrophiles to the anion so generated and provide a wider reaction window in regard to temperature. This results in better regiocontrol and monoalkylation. Significant amounts of dialkylated material were observed earlier on reaction of the anion of methyl ester **7a** with electrophiles.[14] In order to successfully monoalkylate **7b** in high yield, the reactivity of the alkyl halide, the reaction time, and the temperature can be varied to achieve the desired conversion. The versatility of this process has also been amply demonstrated by substitution of biacetyl (**5b**) or cyclohexane-1,2-dione (**5c**), respectively, for glyoxal (**5a**) during the Weiss reaction (Scheme I). Execution of the alkylation sequence at −25 °C resulted in the formation of the dimethyl- and cyclohexyl-*cis*-bicyclo[3.3.0]octanediones **10** and **11** (see the table). Successful manipulation of these intermediates has culminated in the synthesis of 1,10-dimethyltriquinacene (**3**)[15] and the first centrosubstituted triquinacene, 1,10-cyclohexanotriquinacene.[16]

Table I. Monoalkylation: Reaction of 7 with Electrophiles at Low Temperatures, Followed by Hydrolysis-Decarboxylation

electrophile	product[a]	equiv of base	reaction time, temp	yields, %
CH_3I	 **9a**	1.1	3 h, −60 to −50 °C	82
CH_3CH_2I	 **9b**	1.1	3 h, −60 to −50 °C	78
	 **9c**	3	5 h, −60 to −50 °C	90
	 **9d**	2	4 h, −50 to −60 °C	80
	 **10**	2.6	7 h, −25 °C	93
	 **11**	2.2	7 h, −25 °C	82

[a] These 2-substituted derivatives exist as a mixture of exo/endo stereoisomers in an approximate ratio of 3:1. [b] These 2-substituted derivatives exist as a mixture of endo/exo stereoisomers in a ratio of 3:2. For a detailed experimental procedure see ref 15.

Regiospecific alteration of the symmetry of the *cis*-bicyclo[3.3.0]octane-3,7-dione unit **1** by the monoalkylation sequence described above amplifies the versatility of the Weiss reaction for the construction of polyquinenes of complex structure. The high yield synthesis of congeners **9a–d** as well as **10**, should make these materials readily available for the synthesis of cyclopentanoid natural products.[2] Further work to exploit this technology will be reported in due course.

Experimental Section[17]

General Procedure for the Monoalkylation of 7b. To a

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suspension of potassium hydride (0.136 g, 3.39 mmol, 1.13 equiv) in dry DMF (3 mL) under an argon atmosphere was added bis(enol ether) **7b** (1.69 g, 3 mmol) in dry DMF (15 mL) at −20 °C. The solution was stirred for 1 h at −20 °C, after which it was cooled to −70 °C (dry ice/hexane) and methyl iodide (0.5 mL, 8.03 mmol) was added. The mixture was stirred for 3 h at −60 to −50 °C, after which the reaction mixture was allowed to warm to −30 °C and water (5 mL) was added, followed by dilute HCl (1 N, 50 mL). The mixture was extracted with $CHCl_3$ (3 × 50 mL), and the combined layers were washed with H_2O (2 × 50 mL), brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave 1.45 g (82%) of an oily product, which was used directly for hydrolysis.

General Procedure for the Hydrolysis of 8. Method A. Decarboxylation was effected by heating the alkylated material **8** (2.5 mmol) in a mixture of glacial acetic acid (15 mL) and aqueous HCl (15 mL, 1 N) at reflux. After being heated for 2 h, the reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with aqueous $NaHCO_3$ solution (10% w/w) and dried ($MgSO_4$). The solvent was removed under water aspirator pressure to provide an oil, which was further purified by column chromatography over silica gel (20:80 ethyl acetate/hexane) to give pure **9**.

Method B.[18] The alkylated material **8** (2 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with trifluoroacetic acid (7 mL) at room temperature for 1 h. The solvent was removed under reduced pressure to provide an oil, which was dissolved in dioxane (30 mL), treated with aqueous HCl (7.5 mL, 1 N), and then heated at reflux for 2.5 days. The reaction mixture was cooled, concentrated under reduced pressure, diluted with water (20 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, washed with aqueous $NaHCO_3$ (10% w/w) solution, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil, which was further purified by column chromatography (silica gel, 15 g) to give pure monoalkylated *cis*-bicyclo[3.3.0]octane-3,7-dione **9**.

2-Methyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9a). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 2930, 1735, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05, and 1.15 (3 H, 2 s), 1.70–2.10 (2 H, m), 2.20–2.80 (5 H, m), 2.90–3.20 (2 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 219.0, 217.9, 48.01, 44.85, 43.47, 43.40, 43.04, 33.95, 13.21; mass spectrum (CI, CH_4), *m/e* 153 (M + 1, 100); high-resolution mass spectrum calcd for $C_9H_{12}O_2$ 152.0837, found 152.0836.

2-Ethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9b). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 2950, 1730, 1400, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.00 (3 H, m), 1.40–3.20 (11H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 219.25, 218.00, 54.40, 44.23, 43.74, 43.61, 42.28, 34.40, 22.69, 11.50; mass spectrum (CI, CH_4) *m/e* 167 (M + 1, 100); high-resolution mass spectrum calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0997.

2-Allyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9c). This material was obtained as a mixture of epimeric isomers at position **2**: IR (neat) 2920, 1725, 1630, 1140, 900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.90–2.80 (9 H, m), 2.90–3.20 (2 H, m), 4.90–5.10 (2 H, m), 5.70–5.90 (1 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 218.10, 217.65, 134.66, 117. 33, 52.41, 43.69, 43.30, 41.73, 34.01, 33.49; mass spectrum (CI, CH_4), *m/e* 179 (M + 1, 100), 137 (9.1). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 74.19; H, 7.86.

2-Propargyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9d). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 3300, 1740, 1400, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70–2.20 (2 H, m), 2.30–2.90 (8 H, m), 2.95–3.20 (2 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 217.63, 216.59, 80.59, 70.34, 50.86, 43.84, 43.23, 41.87, 34.12, 17.95; mass spectrum (CI, CH_4), *m/e* 177 (M + 1, 100); high-resolution mass spectrum calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0835.

Acknowledgment. We wish to thank the NSF (Grant CHE-8604443) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research. The technical skills of Anju Gupta in the preparation of this manuscript are also gratefully acknowledged.

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The Inverse Electron Demand Diels–Alder Reaction of 3-(Methylsulfonyl)-1,2,4-triazine and Enamines: Isolation of Crystalline Intermediates and an Improved Synthesis of 1-(Methylsulfonyl)tetrahydroisoquinolines

B. L. Chenard* and R. T. Ronau

Central Research, Pfizer Inc., Groton, Connecticut 06340

Gayle K. Schulte[1]

Chemical Instrumentation Center, Yale University, New Haven, Connecticut 06511

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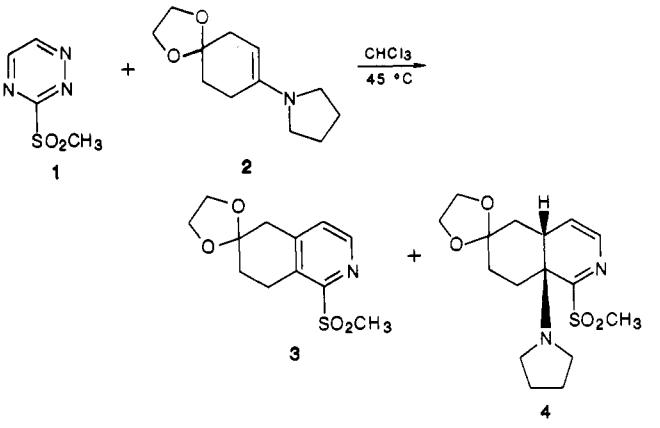
In connection with other work, we required tetrahydroisoquinolines and pursued these targets with the inverse electron demand Diels–Alder reaction of 1,2,4-triazines and enamines, a process that has been developed by Boger[2] and more recently by Taylor.[3] Although the procedure works well for acyclic and cyclopentyl enamines, it has been reported to give only poor yields with cyclohexyl enamines.[4] Therefore it was not surprising that when we reacted triazine **1**[3] and **2** under the standard conditions (chloroform, 45 °C) a miserable yield of tetrahydroisoquinoline **3** (15%) was obtained. In addition to **3**, we also obtained another crystalline product, which we tentatively identified as **4** (20%) on the basis of its NMR spectrum and elemental analysis.



There have been three reports[5] implicating structures such as **4** as intermediates in triazine cycloadditions, but none give any spectral or analytical data to support the structure. Also, the stereochemistry of **4** could have some mechanistic implications regarding the inverse electron

(1) Address inquires regarding the X-ray structure determination to this author.
(2) For a review see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
(3) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2415.
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