p-Methoxy-α-phenylbenzylamine (9). Similar treatment of 2.00 g (15.0 mmol) of 4-methoxybenzonitrile and 6.0 mL (18.0 mmol, 3 M in THF) of phenylmagnesium bromide, as described for **1** except that the alkylation mixture was refluxed for only 14 h and only 285 mg (41.3 mmol, 15 pieces) of lithium was used for the reduction, afforded 2.95 g of a yellow oil. Following Kugelrohr distillation (bp 132–138 °C, 0.1 torr), 2.56 g (12.0 mmol, 80%) of **9** was obtained as a colorless oil:[22] IR ($CHCl_3$) 3440, 3400, 3080, 3040, 3025, 2980, 2960, 2930, 2855, 1685, 1620, 1595, 1515, 1500, 1470, 1460, 1310, 1250, 1180, 1040, 915, 845, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 7.40–7.14 (7 H, m), 6.83 (2 H, dd, J = 6.7 and 2.1 Hz), 5.03 (1 H, s), 3.69 (3 H, s), 2.16 (2 H, br s, exchanges with D_2O); mass spectrum (17 eV), m/z (relative intensity) 214 (6), 213 (M^+, 51), 212 (14), 197 (23), 182 (10), 137 (8), 136 (100), 135 (31), 121 (9), 106 (9), 105 (40).

(22) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289–294.

Acknowledgment. We are grateful to Hoechst-Roussel Pharmaceuticals Inc., Hoffmann-La Roche Inc., Rutgers University (Charles & Johanna Busch Memorial Fund), and the NIH (MBRSG and BRSG programs) for supporting this research. We also thank M. N. Agnew and A. Rizwaniuk, Hoechst-Roussel, Somerville, NJ, for the NMR spectra and MS data.

Regioselectivity of Electrophilic Additions to 7-Oxabicyclo[2.2.1]heptenes Controlled by Remote Substituents. Arenesulfonyl Substituted 7-Oxabicyclo[2.2.1]heptenes as Stereo- and Regioselective Chiral Dienophiles[1]

Kersey A. Black[2] and Pierre Vogel*

Institut de chimie organique de l'Université, CH-1005 Lausanne, Switzerland

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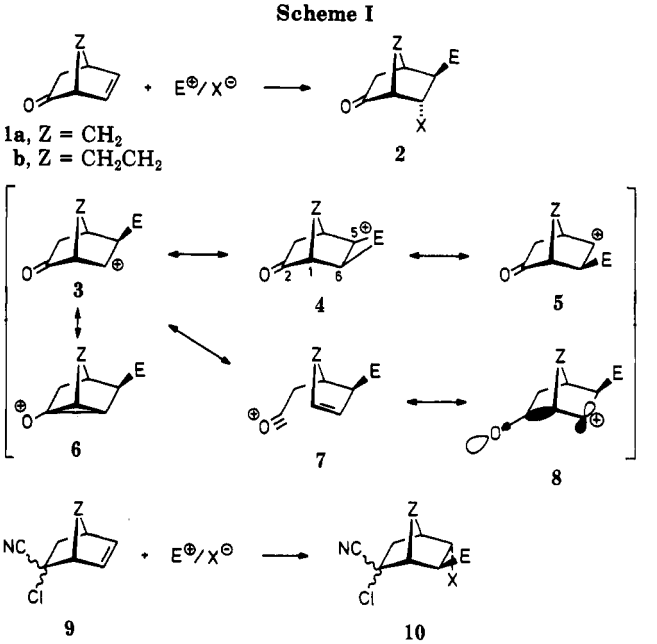
Benzeneselenenyl, 2-nitrobenzenesulfenyl, and 2,4-dinitrobenzenesulfenyl chlorides added to 2-*endo*-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile (**11**) in an anti fashion with complete stereo- and regioselectivity, giving the adducts **13a–c** in which the chlorine substituent occupies the endo position at C(5). Opposite regioselectivity was observed when the same electrophilic reagents were allowed to react with the closely related enone **12** (7-oxabicyclo[2.2.1]hept-5-en-2-one), leading to adducts **14a–c** in which the chloride substituent is endo at position C(6). This stereo- and regiochemical control was used in the preparation of the new chiral bicyclic dienophiles **30** (6-(2-nitrobenzenesulfonyl)-2-*endo*-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile) and **33** (5-benzenesulfonyl-7-oxabicyclo[2.2.1]hept-5-en-2-one), whose cycloadditions to the Danishefsky diene **22** were found to be highly regio- and stereoselective. This allowed the facile preparation of complex bicyclo[4.4.0]decane derivatives in a stereocontrolled fashion.

Under kinetic control, 2-bicyclo[2.2.1]hept-5-enone (**1a**) and 2-bicyclo[2.2.2]oct-5-enone (**1b**) add soft electrophiles, EX, to give the corresponding adducts **2** with high regioselectivity.[3] The nucleophile's (X^-) preference to attack

Scheme I



carbon center C(6) of intermediate **4** can be understood by recognizing that limiting structure **3** is favored over structure **5**. Structure **3** is stabilized due to the carbonyl group's polarizability, which can be interpreted in terms

(1) A preliminary communication of this work has been presented at the 179th ACS Meeting, Sept 8–13, Chicago, Abstr. No. 62, ORGN. For other examples of chiral dienophiles, see, for instance: (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778–4779. Evans, D. A.; Chapman, K. T. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263, and references cited therein. Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737–738. Posner, G. H.; Harrison, W. *Ibid.* **1985**, 1786–1787. Horton, D.; Machinami, T.; Takagi, Y.; Bergmann, C. W.; Christoph, G. C. *Ibid.* **1983**, 1164–1166. De Lucchi, O.; Marchioro, C.; Valle, G.; Modena, G. *Ibid.* **1985**, 878–880. Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727–1728. Sundin, A.; Frejd, T.; Magnusson, G. *Ibid.* **1985**, *26*, 5605–5608. Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279 and references cited therein. Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106–1107. (b) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404. (c) Tolbert, L. M.; Mahfuza, B. A. *Ibid.* **1984**, *106*, 3806–3810. Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112–114. Ortuno, R. M.; Corbera, J.; Font, J. *Tetrahedron Lett.* **1986**, *27*, 1801–1804. Oppolzer, W.; Chapuis, C. *Ibid.* **1983**, *24*, 4665–4668. Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Tattichi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4686–4690. Angell, E. C.; Fringuelli, F.; Halls, T. D. J.; Pizzo, F.; Porter, B.; Taticchi, A.; Tourris, A. P.; Wenkert, E. *Ibid.* **1985**, *50*, 4691–4696. Angell, E. C.; Fringuelli, F.; Pizzo, F.; Poster, B.; Taticchi, A.; Wenkert, E. *Ibid.* **1985**, *50*, 4696–4698. Arai, Y.; Kuwayama, S.-i.; Takeuchi, Y.; Kuizimi, T. *Tetrahedron Lett.* **1985**, *26*, 6205–6208.

(2) Present address: Department of Chemistry, University of Oregon, Eugene, OR.

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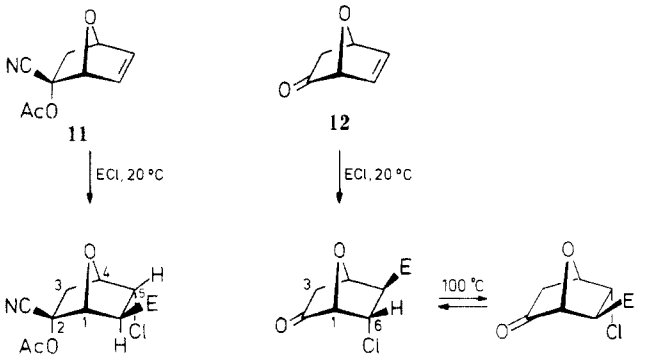
0022-3263/86/1951-5341$01.50/0

Scheme II



of homoconjugation **3** ↔ **6** and/or hyperconjugation **3** ↔ **7** (n(CO) ↔ σC(2),C(1) ↔ pC(6), see **8**). These electron-donating interactions overwhelm the destabilizing field effect of the oxo group. This interpretation has found support in a large body of theoretical[4] and experimental data.[3,5-7] In contrast with **1a** and **1b**, their synthetic precursors, **9a** and **9b**, were found to add soft electrophiles, EX, with the opposite regioselectivity, as indicated by reaction **9** → **10** (Scheme I).[3]

Derivatives of 7-oxabicyclo[2.2.1]heptane have proved to be convenient starting materials in the synthesis of many natural products and materials of biological interest.[9] The availability of systems such as **11** has recently been dramatically improved through the Diels–Alder reaction of 1-cyanovinyl acetate to furan in the presence of Cu(II)[10] or Zn(II)[11,12] salts. Saponification of **11** gives enone **12**, and the optically pure enantiomers of both **11** and **12** can be readily obtained.[11,12] We now report that the utility of these materials as synthetic intermediates is substantially enhanced because electrophiles add to their endocyclic C=C double bond in a stereo- and regiospecific fashion, analogous to the selectivities observed for the additions to **1a** and **9a**.[3] Importantly, it was found that by changing the substituent at C(2) from the acetoxy nitrile in **11** to the carbonyl group in **12**, the regiochemical sense of these additions was completely reversed, giving exclusively adducts **13** and **14**, respectively. Thus, the stereocontrolled functionalization of C(5) and C(6) is possible, and it will be shown that these adducts can be further transformed into new chiral dienophiles of synthetic interest because of their stereo- and regioselective cycloadditions to asymmetric dienes.

Results and Discussion

The electrophilic additions of benzeneselenenyl chloride (**A**), 2-nitrobenzenesulfenyl chloride (B), and 2,4-dinitrobenzenesulfenyl chloride (C) to **11** and **12** gave the corresponding adducts **13** and **14**, respectively, (Scheme II) in good yields. In all cases the electrophilic additions proceeded with complete regio- and stereospecificity (360-MHz ^1H NMR of the mother liquors), with the electrophile attacking the exo face of the C=C double bond and the counterion, Cl^-, adding to the endo face to give the products of anti addition. Control experiments by ^1H NMR showed the almost complete disappearance of **11** after 1 day when a molar, equimolar mixture of **11** and A was allowed to react at 20 °C in $CHCl_3$. Under the same conditions the reaction with B was about 10 times slower. The addition of C required CH_3CN as a solvent, and the reaction was ended after ca. 11 days. Under the same conditions, the enone **12** reacted at least twice as fast as **11**. The adducts **13** and **14** were stable at 20 °C and for several hours in boiling $CHCl_3$. When heated in a more ionizing solvent such as CD_3CN, **14a** was isomerized slowly into the regioisomer **14′a**.[13] The equilibrium **14a**/**14′a** ca. 1.1 was reached after heating to 100 °C for 50 h. The isomerization was accompanied by some decomposition. Saponification of **13a** afforded **14′a**,[13] which was converted to the equilibrium mixture of **14a**/**14′a** on heating to 100 °C in CD_3CN. These experiments confirmed that the selectivities **11** → **13** and **12** → **14** are due to kinetic control. Thus, the regiochemistry of the electrophilic additions of 7-oxabicyclo[2.2.1]hept-5-enes is found to be controlled by the homoallylic substituents at position C(2), and this regiochemistry can be reversed by changing the nature of this substitution.

The structures of adducts **13** and **14** were given by their 360-MHz ^1H NMR spectra with the help of double irradiation experiments. The protons in the exo position at C(3), C(5), and C(6) couple with the adjacent bridgehead proton ($^3J_{H,H}$ = 3–5 Hz), whereas the corresponding endo protons do not.[14] This criterion was used to distinguish the signals of the bridgehead protons H-C(1) and H-C(4) and the relative configuration (exo vs. endo) of the protons H-C(5) and H-C(6). The distinction between H–C–Cl and H–C–Se or H–C–S signals was based on their difference in chemical shifts, the former being generally more deshielded than the latter. The proposed structures **13** and **14** agreed with the expected exo face attack on the C(5)=C(6) double bond in **11** and **12** by the electrophilic reagent.[15] Confirmation of the regiochemistry of **13** and

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(7) Acetals can also be electron-donating homoconjugated substituents[3] because of the hyperconjugative n(O),σ,π interaction. The latter is related to the Grob Fragmentation and the frangomeric effect.[8]
(8) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660–1666. Fischer, W.; Grob, C. A. *Ibid.* **1978**, *61*, 1588–1608. Grob, C. A. *Angew. Chem.* **1976**, *88*, 621–627. See also: Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1–9. Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499–1509. Gleiter, R. *Angew. Chem.* **1974**, *86*, 770–788. Heilbronner, E.; Schmelzer, A. *Helv. Chim. Acta* **1975**, *58*, 936–967.
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(12) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865–1871.
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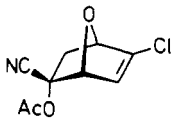
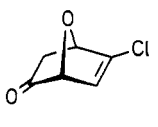
14 was given by the following experiments.

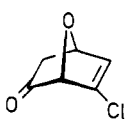
Treatment of **13a** with aqueous H_2O_2 (30%) (0 °C, then 20 °C) gave the chloroalkene **15** in 91% yield. Methanolysis of **15** (MeOH, MeONa) followed by treatment with formalin afforded the chloro enone **16** (87%). On treating **14a** with 1 molar equiv of metachloroperbenzoic acid (*m*-CPBA, −70 °C, then 20 °C), the isomeric chloro enone **17**



15



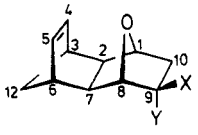
16



17

was obtained (78%, isolated). The Baeyer–Villiger oxidation of the ketone was a minor process under these conditions. In each of the oxidative eliminations **13a** → **15** and **14a** → **17** a single regioisomer was produced. The 6-chloro ketone **17** proved to be quite sensitive; polymerization and darkening was rapid at ambient temperature in either the condensed state or in solution. The 5-substituted isomer **16** was much less sensitive. The structures of **16** and **17** were given unambiguously by their ^1H NMR spectra. For **16** both H-C(1) (^3J(H-C(1),H-C(6)) = 2.25 Hz) and H-C(4) ($^3J(H_{exo}$-C(3),H-C(4)) = 4.25 Hz, $^3J(H_{endo}$-C(3),H-C(4)) ≃ 0 Hz[14]) resonated as doublets. In the case of the ^1H NMR spectrum of **17**, H-C(1) appeared as a broad singlet and H-C(4) as a multiplet ($^3J(H_{exo}$-C(3),H-C(4)) = 4.25 Hz, ^3J(H-C(4),H-C(5)) ≃ 2.0 Hz).

The 7-oxanorbornenes **11** and **12** were dienophiles that added to cyclopentadiene at room temperature. The acetoxy carbonitrile **11** afforded a 93:7 mixture of adducts **18** and **19** resulting from the exo face attack of the C(5)=C(6) double bond. No trace of adducts resulting from attack on the endo face could be detected in the crude reaction mixture (^1H NMR). Adducts **18** and **19** were separated and purified by a combination of crystallization and low pressure liquid chromatography. From enone **12** a 9:1 mixture of adducts **20** and **21** was formed together

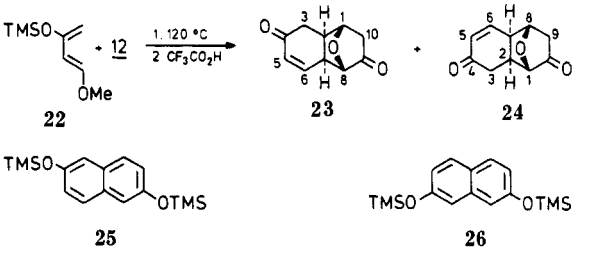


18 X = CN, Y = OAc **19**
20 X, Y = O **21**

with a trace amount of a compound that could not be isolated but whose ^1H NMR characteristics suggested it to be an adduct resulting from the cyclopentadiene addition to the C=C double bond of **20**. The Diels–Alder addition of **12** was also found to be strongly exo face selective.

The structures of adducts **18–21** were easily determined on the basis of 360-MHz ^1H NMR analysis.[14] The bridgehead protons at C(1) and C(8) showed no coupling with the adjacent H-C(2) and H-C(7) as expected for endo protons.[14] The distinction between the isomeric pairs **18**, **19** and **20**, **21** was done on the basis of the vicinal coupling constants between the protons at C(2) and C(7) and the bridgehead protons at C(3) and C(6), respectively. This coupling in adducts **18** and **20** was about 4 Hz, whereas in adducts **19** and **21** there was essentially no coupling between these protons.

The thermal (80–120 °C) cycloaddition of the Danishefsky diene **22** to **11** was a slow and sluggish reaction, which could not compete with the cycloreversion of **11** into furan and 1-cyanovinyl acetate. The course of the reaction was not improved by the presence of Lewis acids (ZnI_2, $BF_3{\cdot}Et_2O$). The thermal reaction (sealed tube, toluene, 120 °C) of enone **12** with **22** gave a complex mixture. Exam-



22 **23** **24**

25 **26**

ination of it with 360-MHz ^1H NMR indicated the presence of a mixture of stereoisomers resulting from the attack of the exo face of **12**. These spectra did not allow for identification of the individual isomers, nor quantification of their relative abundance. Treatment of the crude reaction mixture with CF_3COOH (20 °C, 1 h) led to complete hydrolysis of the enol ethers and concomitant elimination of 1 molar equiv of MeOH to give a 3:1 mixture of enones **23** and **24**. A small percentage of the products resulting from the addition of **22** to the carbonyl functions in **12** and **23** was also found,[16,17] as indicated by the ^1H NMR spectrum of the crude mixture of enones **23** + **24**, which showed signals at 5.3–5.5 ppm and at 7.2–7.4 ppm (AB pattern, $J_{H,H}$ = 6 Hz), characteristic of 2,3-dihydro-γ-pyrone structure.[18]

The two regioisomers **23** and **24** were separated by a combination of low pressure chromatography on silica gel and crystallization. ^1H and ^{13}C NMR, as well as the other spectra data, did not allow definitive assignment of their respective structures, so a chemical method was sought to establish their respective identities. This was achieved through opening of the oxygen bridge under basic conditions.[1b,19] The bridge would not open until a very strong silylating reagent was added. Conditions of excess Me_3SiCl and Et_3N in $CHCl_3$ (50 °C, 15 h) gave no reaction, whereas with Me_3SiOTf and Et_3N in $CHCl_3$ the reaction was over after 2 min at 0 °C, effectively transforming enones **23** and **24** into naphthalene derivatives **25** and **26**, respectively. The ^1H NMR spectra of these two isomers were compared with that of an authentic sample of the 2,7-disubstituted isomer, prepared from the corresponding commercial naphthalene-2,7-diol. Thus, it was established that the major adduct resulting from the cycloaddition **12** + **22** is that expected on the basis of the ketone function behaving as a remote electron-withdrawing group. Evidently there is insufficient electron demand in this reaction to force the

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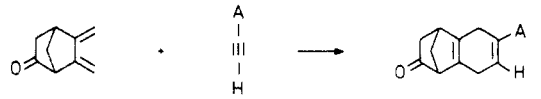
carbonyl group to participate as an electron donor, a role it accepts in the electrophilic additions to **12** (and **1**). It is interesting to note here that the Diels–Alder additions of dienone **27** to strong dienophiles (with a "normal" electron demand) give the "para" adducts **28** as a major product, in agreement with the hypothesis of the homoconjugated carbonyl group acting, in this case also, as an electron-donating substituent.[6]

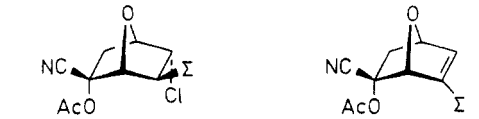


27 **28** (major)

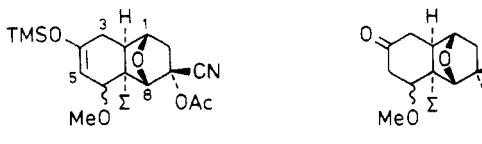
Many attempts were made to catalyze its cycloaddition with **22**, with the hope of augmenting the observed thermal reactivity and regioselectivity of the homoconjugated enone **12**. No reaction was observed in the presence of catalysts such as $EtAlCl_2$, $BF_3{\cdot}Et_2O$, and $TiCl_4$ (up to 1.5 molar equiv of catalyst), commonly in CH_2Cl_2 at −70 °C. At higher temperatures polymerization of **22** was a predictable problem while **12** proved fairly stable to these catalysts. ^1H NMR analysis of the crude reaction mixtures after workup in the presence of acid indicated the formation of small amounts of the spiro pyrone resulting from the cycloaddition to the carbonyl function in **12**.

The modest yield and low regioselectivity of the Diels–Alder addition **12** + **22** led us to examine the reactions of the chlorinated enones **16** and **17** with **22**. For both **16** and **17** the cycloadditions proved to be as slow as for **12** + **22** (17 h, 120 °C, 1.25 molar equiv of **22**, in a minimum of toluene), and 360-MHz ^1H NMR analysis of the crude reaction material showed a mixture of expected adducts. Treatment with acid resulted in a complex mixture of products resulting from enol ether hydrolysis, followed by HCl elimination, MeOH elimination, and aromatization. The reaction conditions suggested that the chlorine substituent in **16** and **17** did not augment significantly the dienophilicity of the bicyclic olefin and was probably not dramatically effective in controlling the regiochemistry of the addition. Tentative product assignments agreed with this interpretation. Inspired by the works of Böll et al.[20] and Paquette et al.,[21] we envisioned preparing more activated dienophiles in the way described below.

Treatment of adduct **13b** with 2.5 molar equiv of metachloroperbenzoic acid ($CHCl_3$, 0–20 °C, 4 days) gave the corresponding sulfone **29** almost quantitatively. Elimination of HCl (DBU, $CHCl_3$, 0 °C)[22] furnished the olefin **30** in 98% yield. Danishefsky's diene (**22**) added to **30** under relatively mild conditions (CH_3CN, 75 °C, 2 h) with complete regiospecificity, giving a 3:1 mixture of stereoisomers of **31** with respect to the methoxy substituent at C(6). More importantly, the regiochemistry of the cycloaddition was completely controlled by the sulfonyl group and the diene attack occurred exclusively on the exo face of **30**, as anticipated.[20]



29 **30**



31 **32**

The initial strategy for making the enone **33b** with a sulfone group in position C(5) first required protection of the ketone as a ketal, thus protecting it during the two subsequent steps: oxidation of the sulfide into the sulfone and elimination of HCl under basic conditions. All attempts to form a ketal of ketone **14b** failed due to no reaction, presumably because of steric hindrance resulting from the *endo*-chloro substituent at C(6). Other means to generate the desired vinyl sulfone were therefore sought.

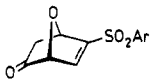
The addition of phenylselenenyl phenyl sulfone ($PhSeSO_2Ph$) to alkenes can, in principle, be induced thermally, catalytically in the presence of Lewis acids, or photochemically.[23,24] Reports suggest also that the regiochemistry can sometimes be controlled in additions to unsymmetrically substituted olefins.[24] The catalytic additions ($BF_3{\cdot}Et_2O$, PhH, 20 °C) of $PhSeSO_2Ph$ to **11** and **12** were slow reactions, giving mixtures of adducts and polymerized material. The photochemical addition of $PhSeSO_2Ph$ to **11** proved to go very slowly, giving mainly products resulting from reaction of the reagent with itself, as well as unreacted **11**. On the other hand, the photochemical addition of $PhSeSO_2Ph$ to enone **12** proceeded much more quickly (Hg-arc, λ_{irr} >355 nm, PhH), giving mostly the desired 5-*exo*-sulfonyl-6-*endo*-selenenyl derivative **34** (>80% of the isolated adducts). The regioselectivity of this addition was difficult to quantify exactly due to the instability of the product formed and their partial decomposition. Nevertheless, attempts to isolate the possible 6-phenylsulfonyl derivative in the crude reaction product did not meet with success. Treatment of the crude adduct mixture with methachloroperbenzoic acid gave after workup enone **33a** analytically pure in moderate yield (32% from **12**). More work is required to understand the regioselectivity of the photochemically induced addition **12** + $PhSeSO_2Ph$.

The bicyclic dienophile **33a** also readily added to **22** (80 °C, 2.5 h), giving a mixture of trimethylsiloxy enol ethers **35** (stereoisomeric at the OCH_3 substituted carbon). Treatment of this mixture with dilute acid (0.5 N HCl, THF, 1:3, 30 min) gave a mixture of three products in essentially quantitative yield. A 1:1 mixture of the two diastereomeric β-methoxy ketones **36** constituted 90% of the reaction product, with the remaining 10% being the corresponding enedione **37** resulting from the elimination of methanol. Further treatment with strong protic acids (TFA, 60 °C, 18 h) did not result in further elimination of methanol. When the initial reaction mixture of **35** was treated with $BF_3{\cdot}Et_2O$ in toluene (0 °C, 30 min), a 2:1 mixture of **37** and **36** was obtained, flash chromatography affording the pure enedione **37**. These results show clearly that the sulfone at C(5) controlled completely the regiochemistry of the cycloaddition.

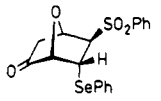
Conclusion

Electrophilic reagents have been shown to add to the olefin in **11** and **12** regiospecifically, with the sense of the

(20) Böll, W.; König, H. *Liebigs Ann. Chem.* **1979**, 1657–1664. Böll, W. *Ibid.* **1979**, 1665–1674.
(21) Paquette, L. A.; Crouse, G. D. *J. Org. Chem.* **1983**, *48*, 141–142, and references cited therein. See also: Gritsenko, E. I.; Butenko, G. G.; Plemenkov, V. V. *Zh. Org. Khim.* **1984**, *20*, 741–746.
(22) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208–1217.
(23) Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, *21*, 2213–2214, 2215–2218. Gancarz, R. A.; Kice, J. L. *Ibid.* **1980**, *21*, 4155–4158; *J. Org. Chem.* **1981**, *46*, 4899–4906.
(24) Back, T. G.; Collins, S. *J. Org. Chem.* **1981**, *46*, 3249–3256.



33a, Ar = C_6H_5
b, Ar = 2-$NO_2C_6H_4$



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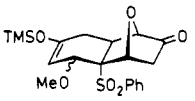

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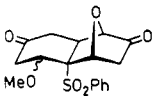

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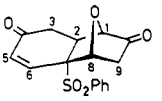

37

addition completely controlled by the nature of the remote substituent at C(2). In addition, the 7-oxabicyclo[2.2.1]-hept-5-enes, derivatives **11** and **12** have been transformed in a stereospecific fashion into the chiral vinyl sulfonyl derivatives **30** and **33a**, respectively. The latter add to nonsymmetrical dienes such as Danishefsky's diene **22** with high stereoselectivity, because of the bicyclic nature of the dienophiles, and with high regioselectivity because of the directing effect of the arenesulfonyl substituents. The methodology developed here allows the stereoselective construction of polyfunctional bicyclo[4.4.0]decanes that are not readily available otherwise. Since the starting 7-oxabicyclo[2.2.1]heptenes **11** and **12** can be prepared optically pure,[11,12] this technology should be applicable in the synthesis of many natural compounds.[1]

Experimental Section

Melting points (uncorrected) were determined on a Tottoli apparatus, and for bulb-to-bulb distillations (Buchi apparatus) the temperature reported refers to the oven temperature.

Routine ^1H NMR spectra were obtained on a Bruker WP 80 instrument (80 MHz), while high field proton spectra and all ^{13}C NMR spectra were obtained on a Bruker WH-360 FT instrument (Aspect 2000 computer, 32 K memory space) operating at 360 MHz or 90.55 MHz, respectively. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (Me_4Si), using either Me_4Si (δ_H 0.00, δ_C 0.00) or the solvent's residual proton signal (chloroform-*d*: δ_H 7.24, δ_C 77.0; benzene-d_6: δ_H 7.15, δ_C 128.5; acetone-d_6: δ_H 1.95, δ_C 29.8; acetonitrile-d_3: δ_H 2.05, δ_C 1.3; or dimethyl sulfoxide-d_6: δ_H 2.50, δ_C 39.5) as an internal reference. Also reported are the apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons (when appropriate), coupling constants (hertz), and tentative structural assignment. Other spectral data and elemental analyses are provided as supplementary material.

Solvents were either reagent or technical grade and when necessary were purified and dried by distillation from an appropriate desiccant under an atmosphere of N_2. Concentration of solutions after reactions and extractions involved use of a rotary evaporator operating at reduced pressure of approximately 20 torr, and organic solutions were commonly dried over anh $MgSO_4$ unless otherwise stated.

2-*endo*-Acetoxy-6-*exo*-benzeneselenenyl-5-*endo*-chloro-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (13a). To a solution of acetoxy nitrile **11** (1.00 g, 5.6 mmol)[11] in $CHCl_3$ (5 mL) was added a solution of PhSeCl (1.07 g, 5.6 mmol) in $CHCl_3$ (10 mL), and the resulting red-brown mixture was stirred at room temperature for 3 days, after which the color had changed to a light yellow. It was diluted with CH_2Cl_2 (25 mL) and then washed with 5% aqueous Na_2CO_3 (2 × 15 mL), H_2O (2 × 15 mL), and brine (1 × 15 mL) before being dried ($MgSO_4$), filtered, and concentrated to yield 2.24 g of a light yellow oil. This consisted in a single stereoisomer and this product was crystallized from a mixture of Et_2O and petroleum ether (1:1) at −20 °C to give 1.72 g (83%) of crystalline material: mp 71–71.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.61 (m, 2 H, H-aromatic), 7.35 (m, 3 H, H-aromatic), 5.08 (br s, H-C(1)), 4.69 (m, H-C(4)), 4.17 (dd, J = 5.0, 4.5, H-C(5)), 3.40 (d, J = 4.5, H-C(6)), 2.64 (m, 2 H, J = 3.0, H-C(3)), 2.05 (s, 3 H, CH_3).

2-*endo*-Acetoxy-5-*endo*-chloro-6-*exo*-(2-nitrobenzenesulfenyl)-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (13b). To a solution of **11** (5.37 g, 30 mmol) in $CHCl_3$ (25 mL) at room temperature was added 2-nitrobenzenesulfenyl chloride (5.69 g, 30 mmol) as a solution in $CHCl_3$ (50 mL), and the resulting yellow solution was stirred at ambient temperature for 12 days during which a precipitated formed. Ether (150 mL) was added and the solution filtered to give 9.85 g of bright yellow powder. The filtrate was concentrated and dissolved in a minimum amount of $CHCl_3$, and additional product (0.74 g) was precipitated from solution by the addition of ether. The combined material (10.58 g, 95.6%) was used without further purification. Crystallization from acetone provided an analytical sample: mp 171.5–173 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 8.21, 7.63, 7.47, 7.43 (m, 4 H, H-aromatic, 4.95 (s, H-C(1)), 4.86 (dd, J = 5.0, 4.5, H-C(4)), 4.18 (dd, J = 5.0, 4.25, H-C(5)), 3.82 (d, J = 4.25, H-C(6)), 2.77 (m, 2 H, $H_2C(3)$), 2.27 (s, 3 H, $COCH_3$).

2-*endo*-Acetoxy-5-*endo*-chloro-6-*exo*-(2,4-dinitrobenzenesulfenyl)-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (13c). To a solution of **11** (1.00 g, 5.6 mmol) in CH_3CN (5 mL) was added a solution of 2,4-dinitrobenzenesulfenyl chloride (1.33 g, 5.7 mmol) in CH_3CN (15 mL), and the resulting mixture was stirred at ambient temperature for 11 days. Ether (50 mL) was added and the solution filtered to yield a yellow precipitate (1.43 g, 62%). Concentration of the filtrate provided a brown oil, in which no identifiable products were evident by ^1H NMR analysis. Crystallization from Me_2SO provided an analytical sample: mp 232–235 °C; ^1H NMR (360 MHz, Me_2SO-d_6) δ 9.02, 8.55, 7.77 (m, 3 H, H-aromatic), 5.05 (s, H-C(1)), 5.00 (dd, J = 6.0, 5.0, H-C(4)), 4.38 (ddd, J = 5.0, 4.5, 1.25, H-C(5)), 4.27 (d, J = 4.5, H-C(1)), 2.86 (ddd, J = 15.0, 6.0, 1.25, H_{exo}-C(3)), 2.73 (d, J = 15.0, H_{endo}-C(3)).

5-*exo*-Benzeneselenenyl-6-*endo*-chloro-7-oxabicyclo-[2.2.1]heptan-2-one (14a). A solution of enone **12** (1.10 g, 10.0 mmol in $CHCl_3$ (10 mL) was cooled to 0 °C and stirred under a nitrogen atmosphere while a solution of PhSeCl (1.92 g, 10.0 mmol) in $CHCl_3$ (10 mL) was added dropwise over 15 min. The solution was stirred for an additional 30 min at 0 °C and then overnight at room temperature. The yellow solution was diluted with $CHCl_3$ (20 mL), washed with 5% aqueous Na_2CO_3 (2 × 15 mL), H_2O (2 × 10 mL), and brine (1 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated to give 3.04 g of a light orange oil. Analysis by ^1H NMR of this crude product before purification indicated the presence of only one stereoisomer, which was then crystallized from a mixture of ether and petroleum ether (1:1) at −20 °C to give 2.40 g of **14a** (80%): mp 46.5–47.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63 (m, 2 H, H-aromatic), 7.35 (m, 3 H, H-aromatic), 4.87 (dm, J = 6.0, H-C(4)), 4.46 (dm, J = 5.75, H-C(1)), 4.28 (dddd, J = 5.75, 3.0, 1.0, 1.0, H-C(6)), 3.52 (d, J = 3.0, H-C(5)), 2.63 (ddm, J = 18.0, 6.0, H_{exo}-C(3)), 2.21 (d, J = 18.0, H_{endo}-C(3)).

6-*endo*-Chloro-5-*exo*-(2-nitrobenzenesulfenyl)-7-oxabicyclo[2.2.1]heptan-2-one (14b). A solution of **12** (0.55 g, 5.0 mmol) in $CHCl_3$ (5 mL) was stirred at room temperature while a solution of 2-nitrobenzenesulfenyl chloride (0.95 g, 5 mmol) in $CHCl_3$ (5 mL) was added dropwise. The resulting yellow solution was stirred for 8 days during which time a yellow solid precipitated from solution. Ether (50 mL) was added and the mixture filtered to give 1.09 g (73%) of the product as a yellow solid. Examination, by ^1H NMR, of the brown oil obtained upon concentration of the above filtrate did not reveal the presence of another stereoisomer. Recrystallization from acetone provided an analytical sample: mp 191–192.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 8.26, 7.66, 7.53, 7.40 (4 H, H-aromatic), 4.93 (d, J = 6.25, H-C(4)), 4.58 (d, J = 5.75, H-C(1)), 4.27 (ddd, J = 5.75, 3.0, 1.0, H-C(6)), 3.75 (d, J = 3.0, H-C(5)), 2.78 (dd, J = 18.0, 6.25, H_{exo}-C(3)), 2.44 (d, J = 18.0, H_{endo}-C(3)).

6-*endo*-Chloro-5-*exo*-(2,4-dinitrobenzenesulfenyl)-7-oxabicyclo[2.2.1]heptan-2-one (14c). A solution of **12** (0.55 g, 5.0 mmol) in CH_3CN (5 mL) was stirred at room temperature while a solution of 2,4-dinitrobenzenesulfenyl chloride (1.17 g, 5.0 mmol) in CH_3CN (15 mL) was added dropwise over 10 min. The reaction mixture was cooled to 10 °C and stirred for 1 h before stirring at room temperature for 15 days during which time a green-yellow solid precipitated from solution. Ether (50 mL) was added to the reaction mixture and the solid filtered (1.50 g, 87% crude), which proved to be a single isomer. This very insoluble material was recrystallized from hot CH_3CN (150 mL) to give 1.28 g (74%) of yellow-green crystalline material: mp 216–218 °C; ^1H NMR (360 MHz, CD_3CN) δ 9.03, 8.51, 7.84 (m, 3 H, H-aromatic), 5.01 (d,

J = 6.0, H-C(4)), 4.67 (d, J = 5.5, H-C(1)), 4.46 (dd, J = 5.5, 3.0 (C(6)), 4.15 (d, J = 3.0, H-C(5)), 2.83 (dd, J = 18.0, 6.0, H_{exo}-C(3)), 2.61 (d, J = 18.0, H_{endo}-C(3)).

2-*endo*-Acetoxy-5-chloro-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile (15). To a solution of **13a** (740 mg, 2.0 mmol) in THF (7 mL) stirred at 0 °C was added H_2O_2 (2.06 mL of a 30% aqueous solution, 20 mmol). The mixture was stirred at 0 °C for 1 h and then warmed to room temperature and stirred overnight. It was diluted with H_2O (50 mL) and then extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with 5% aqueous Na_2CO_3 (3 × 10 mL), H_2O (1 × 10 mL), and brine (2 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 4.18 g of colorless oil. This was crystallized from Et_2O/petroleum ether to give 386 mg (91%) of a white crystalline material: mp 89–90 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.06 (d, J = 2.0, H-C(6)), 5.62 (dd, J = 2.0, 1.75, H-C(1)), 4.90 (dd, J = 4.75, 1.25, H-C(4)), 2.83 (dd, J = 13.0, 4.75, H_{exo}-C(3)), 2.10 (s, 3 H, CH_3), 1.94 (d, J = 13.0, H_{endo}-C(3)).

5-Chloro-7-oxabicyclo[2.2.1]hept-5-en-2-one (16). To a solution of **15** (2.13 g, 10.0 mmol) in methanol (15 mL), stirred under an N_2 atmosphere at room temperature, was added sodium methoxide (0.10 mL of MeONa 30% in MeOH, 0.54 mmol). This solution was stirred for 2 h before formalin (2.0 mL of 40% aqueous solution) was added and stirring continued for 3 h. The solution was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated by distillation at atmospheric pressure to give a yellow oil. This was bulb-to-bulb distilled (70 °C, 1 torr) to yield 1.25 g (87%) of **16** as a clear colorless oil: ^1H NMR (360 MHz, $CDCl_3$) δ 6.27 (d, J = 2.25, H-C(6)), 5.06 (d, J = 4.25, H-C(4)), 4.66 (dm, J = 2.25, H-C(1)), 2.33 (dd, J = 16.0, 4.25, H_{exo}-C(3)), 2.05 (d, J = 16.0, H_{endo}-C(3)).

6-Chloro-7-oxabicyclo[2.2.1]hept-5-en-2-one (17). To a solution of **12** (3.01 g, 10 mmol) in CH_2Cl_2 (70 mL), stirred at −70 °C under a nitrogen atmosphere, was added dropwise a solution of *m*-CPBA (1.72 g, 10.0 mmol, 1.92 g of 90% material) in CH_2Cl_2 (30 mL) over 30 min. The solution was stirred at −70 °C for 2 h before being warmed to 20 °C over 3 h and then stirred overnight. It was washed with 5% aqueous Na_2CO_3 (3 × 20 mL), H_2O (2 × 10 mL), and brine (1 × 15 mL) before being dried ($MgSO_4$), filtered, and concentrated by distillation at atmospheric pressure to give an orange oil which was bulb-to-bulb distilled (70 °C, 1 torr) to give 1.12 g (78%) of **17** as a clear colorless liquid: ^1H NMR (360 MHz, $CDCl_3$) δ 6.55 (d, J = 2.0, H-C(5)), 5.41 (ddd, J = 4.25, 2.0, 1.0, H-C(4)), 4.44 (br s, H-C(1)), 2.37 (dd, J = 16.0, 4.25, H_{exo}-C(3)), 2.07 (d, J = 16.0, H_{endo}-C(3)).

(1*RS*,2*SR*,3*RS*,6*SR*,7*RS*,8*RS*,9*SR*)-9-*endo*-Acetoxy-11-oxatetracyclo[6.2.1.1.^{3,6}0^{2,7}]undec-4-ene-9-*exo*-carbonitrile (18). A solution of **11** (0.50 g, 2.80 mmol) in cyclopentadiene (1.00 mL) was stirred at room temperature for 4 h, and aliquots of cyclopentadiene monomer were added periodically (10 × 0.5 mL), until all dienophile had reacted. The reaction mixture was poured onto a short column of silica gel, and after eluting the dimer of cyclopentadiene with petroleum ether, the cycloaddition product was eluted with 40% EtOAc/petroleum ether to give 0.722 g of white solid. Analysis by ^1H NMR indicated the presence of two stereoisomers (93:7). Recrystallization from EtOAc/petroleum ether gave 375 mg of **18**, and the diastereomers remaining in the filtrate were separated by low pressure chromatography (Lobar 60 column) to give an additional 118 mg of **18** and 36 mg of the minor isomer **19**.

The major isomer **18** was recrystallized from Et_2O/petroleum ether to give an analytical sample: mp 124.5–125.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.95 (m, 2 H, H-C(4 and 5)), 5.67 (s, H-C(8)), 5.25 (d, J = 6.0, H-C(1)), 2.89 (m, 2 H, H-C(3 and 6)), 2.56 (dd, J = 13.5, 6.0, H_{exo}-C(10)), 2.53 (dd, J = 8.25, 4.0, H-C(2 or 7)), 2.31 (dd, J = 8.25, 3.75, H-C(2 or 7)), 2.15 (s, 3 H, CH_3), 1.68 (d, J = 13.5, H_{endo}-C(10)), 1.32 (dt, J = 8.25, 1.5, Hr-C(12)), 1.16 (d, J = 8.25, Hs-C(12)).

(1*RS*,2*SR*,3*SR*,6*RS*,7*RS*,8*RS*,9*SR*)-9-*endo*-Acetoxy-11-oxatetracyclo[6.2.1.1.^{3,6}0^{2,7}]undec-4-ene-9-carbonitrile (19). The minor isomer **19** (36 mg) was crystallized in a similar manner to give a white solid: mp 109–110 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.16 (m, 2 H, H-C(4 and 5)), 4.86 (s, H-C(8)), 4.46 (d, J = 5.75, H-C(1)), 2.81 (m, 2 H, H-C(3 and 6)), 2.67 (dd, J = 13.5, 5.75, H_{exo}-C(10)), 2.32 (d, J = 8.0, Hs-C(12)), 2.14 (s, 3 H, CH_3), 1.97 (d, J = 7.0, H-C(2 or 7)), 1.78 (d, J = 13.5, H_{endo}-C(10)), 1.75 (d, J = 7.0, H-C(2 or 7)), 1.06 (dm, J = 8.0, Hr-C(12)).

(1*RS*,2*SR*,3*RS*,6*SR*,7*RS*,8*RS*)-11-Oxatetracyclo[6.2.1.1.^{3,6}0^{2,7}]undec-4-en-9-one (20). A solution of **12** (0.50 g, 4.5 mmol) in cyclopentadiene (1.00 mL) was stirred at room temperature for 4 h, and then portions of cyclopentadiene were added periodically (10 × 0.5 mL) until all dienophile had reacted. The reaction mixture was poured onto a short column of silica gel and eluted with petroleum ether and then with 40% EtOAc/petroleum ether to yield 0.872 g of a clear colorless oil. Analysis by ^1H NMR indicated the presence of the two stereoisomers resulting from exo attack on the dienophile, in a ratio of 90:10. The mixture was subjected to low pressure chromatography on silica gel, to give 783 mg of isomer **20** as a clear oil, which was crystallized from petroleum ether/pentane at −20 °C to give an analytical sample: mp 126–128 °C (sub); ^1H NMR (360 MHz, $CDCl_3$) δ 6.02 (dd, J = 6.0, 3.0, H-C(4 or 5)), 6.00 (dd, J = 6.0, 3.0, H-C(4 or 5)), 4.47 (d, J = 5.75, H-C(1)), 4.03 (s, H-C(8)), 2.97 (m, 2 H, H-C(3 and 6)), 2.53 (dd, J = 8.0, 4.0, H-C(2 or 7)), 2.39 (dd, J = 8.0, 4.0, H-C(2 or 7)), 2.32 (dd, J = 17.0, 5.75, H_{exo}-C(10)), 1.88 (d, J = 17.0, H_{endo}-C(10)), 1.42 (dt, J = 8.25, 1.75, H-C(12)), 1.30 (dm, J = 8.25, H-C(12)).

(1*RS*,2*SR*,3*SR*,6*RS*,7*RS*,8*RS*)-11-Oxatetracyclo[6.2.1.1.^{3,6}0^{2,7}]undec-4-en-9-one (21). Chromatography also provided 88 mg of a volatile oil, which was an impure sample of the minor isomer **21**, which was not purified further: ^1H NMR (360 MHz, $CDCl_3$) δ 6.20 (dd, J = 6.0, 3.0, H-C(4 or 5)), 6.15 (dd, J = 6.0, 3.0, H-C(4 or 5)), 4.62 (d, J = 5.75, H-C(1)), 4.15 (s, H-C(8)), 2.90 (br s, H-C(3 or 6)), 2.85 (br s, H-C(3 or 6)), 2.40 (ddd, J = 17.25, 5.75 1.5, H_{exo}-C(10)), 2.37 (dm, J = 8.5, H-C(12)), 1.94 (d, J = 17.25, H_{endo}-C(10)), 1.92 (d, J = 7.5, H-C(2 or 7)), 1.82 (d, J = 7.5, H-C(2 or 7)).

(1*RS*,2*SR*,7*RS*,8*RS*)-11-Oxatricyclo[6.2.1.0.^{2,7}]undec-5-ene-4,9-dione (23). A degassed solution of **12** (0.55 g, 5 mmol), 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (**22**) (1.08 g, 6.25 mmol), and hydroquinone (2-3 mg) in toluene (1.25 mL) was heated to 120 °C for 20 h in a sealed Pyrex tube. The crude reaction mixture proved to be complex for direct analysis of isomeric composition by ^1H NMR at 360 MHz, so it was taken up in trifluoroacetic acid (5 mL) and stirred at 50 °C for 1 h. The red-black solution was diluted with $CHCl_3$ (50 mL), washed with 5% aqueous $NaHCO_3$ (4 × 20 mL), H_2O (2 × 10 mL), and brine (1 × 15 mL), dried ($MgSO_4$), filtered, and concentrated to give 850 mg of an orange oil.

This material was flash chromatographed to give four fractions: **12** (33 mg, 6%), the spiro addition product resulting from cycloaddition to the carbonyl (28 mg, 3%), a mixture of the two regioisomers **23** and **24** in a ratio of 3:1 (432 mg, 49%), and a product resulting from bis-addition to **12**, at the olefin and at the carbonyl (112 mg, 9%).

The two regioisomers **23** and **24** were separated by a combination of recrystallization and low pressure chromatography on silica gel. To establish their respective structures, the two isomers were individually treated with Et_3N (3 equiv) and Me_3SiOTf (4 equiv) in $CDCl_3$ at 0 °C. Under these conditions a single product formed immediately in each case, the corresponding 2,6- and 2,7-bis(trimethylsiloxy)naphthalene (**25** and **26**). The 360-MHz ^1H NMR spectra of these products were compared to that of an authentic sample of the 2,7-isomer, prepared from commercial 2,7-dihydroxynaphthalene (Et_3N, Me_3SiCl, $CHCl_3$): ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (d, 2 H, J = 9.0, H-C(4 and 5), 7.09 (d, 2 H, J = 2.0, H-C(1 and 8), 6.96 (dd, 2 H, H = 9.0, 2.0, H-C(3 and 6), 0.36 (s, 18 H, Me_3Si); 2,6-Isomer **25**: ^1H NMR (360 MHz, $CDCl_3$) δ 7.61 (d, 2 H, J = 8.75, H-C(4 and 8), 7.17 (d, 2 H, J = 2.25, H-C(1 and 5), 7.06 (dd, 2 H, J = 8.75, 2.25, H-C(3 and 7), 0.33 (s, 18 H, Me_3Si).

The major isomer, **23**, was obtained as a crystalline solid: mp 128.5–129.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.74 (dd, J = 10.25, 4.5, H-C(6)), 6.19 (dd, J = 10.25, 1.75, H-C(5)), 4.63 (d, J = 6.0, H-C(1)), 4.17 (br s, H-C(8)), 2.92 (m, H-C(7)), 2.69 (m, 2 H, C(2 and/or 3)), 2.57 (dddd, J = 17.5, 6.0, 1.25, 0.5, H_{exo}-C(10)), 2.55 (m, H-C(2 or 3)), 2.18 (d, J = 17.5, H_{endo}-C(10)).

(1*RS*,2*RS*,7*SR*,8*RS*)-11-Oxatricyclo[6.2.1.0^{2,7}]undec-5-ene-4,10-dione (24). The minor isomer **24** was also obtained as a crystalline product: mp 120.5–122 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 6.79 (dd, J = 10.25, 4.0 H-C(6)), 6.17 (dd, J = 10.25, 1.75,

H-C(5)), 4.69 (dm, J = 6.0, H-C(8)), 4.14 (br s, H-C(1)), 2.90 (m, H-C(7)), 2.75 (m, H-C(2)), 2.72 (m, H-C(3)), 2.61 (ddm, J = 17.5, 6.0, H_{exo}-C(9)), 2.54 (m, H-C(3)), 2.23 (d, J = 17.5, H_{endo}-C(9)).

2-*endo*-Acetoxy-5-*endo*-chloro-6-*exo*-(2-nitrobenzenesulfonyl)-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (29). A solution of **13b** (3.69 g, 10 mmol) in $CHCl_3$ (80 mL) was cooled to 0 °C under an N_2 atmosphere and a solution of *m*-CPBA (4.30 g, 25 mmol) in $CHCl_3$ (60 mL) was added dropwise over 30 min. In the reaction mixture, stirred at 0 °C for 3 h, a precipitate formed that redissolved on warming the solution to room temperature. During 4 days of stirring at room temperature, the solution slowly lost its yellow color and a white precipitate formed. The solution was diluted with $CHCl_3$ (200 mL), washed with 5% aqueous $Na_2S_2O_5$ (3 × 50 mL), 5% aqueous $NaHCO_3$ (3 × 50 mL), and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to give 4.80 g of white crystalline material. This was powdered as a slurry in ether and the solvent removed in vacuo (to remove trapped chloroform) to yield 4.00 g (99%) of **29**: mp 190–191 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 8.24 (m, 1 H, H-aromatic), 7.90 (m, 3 H, H-aromatic), 5.48 (s, H-C(1)), 4.98 (m, H-C(4)), 4.74 (dd, J = 5.5, 4.5, H-C(5)), 4.52 (d, J = 5.5, H-C(6)), 2.73 (m, 2 H, H-C(3)), 2.17 (s, 3 H, CH_3).

2-*endo*-Acetoxy-6-(2-nitrobenzenesulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile (30). A solution of **29** (4.01 g, 10 mmol) in $CHCl_3$ (250 mL) cooled to 0 °C and stirred under a nitrogen atmosphere was treated with 1,8-diazabicyclo-[4.5.0]undec-7-ene (DBU, 1.60 g, 10.5 mmol, 1.61 mL of 97% purity). The solution was stirred at 0 °C for 20 min and then diluted with $CHCl_3$ (150 mL) and washed with 1.0 N aqueous HCl (4 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to give 3.70 g of **30** as a white solid. This material was recrystallized from acetone to give 3.52 g (96%) of analytically pure material: mp 178–179 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 8.18 (m, 1 H, H-aromatic), 7.88 (m, 3 H, H-aromatic), 7.61 (d, J = 2.0, H-C(5)), 5.68 (s, H-C(1)), 5.36 (dm, J = 5.5, H-C(4)), 2.98 (dd, J = 13.25, 5.5, H_{exo}-C(3)), 2.17 (s, 3 H, CH_3), 2.01 (d, J = 13.25, H_{endo}-C(3)).

(1*RS*,2*RS*,6(*RS* or *SR*),7*RS*,8*SR*,9*SR*)-9-Acetoxy-4-oxo-6-methoxy-7-(2-nitrobenzenesulfonyl)-11-oxatricyclo-[6.2.1.$0^{2,7}$]undecane-2-carbonitrile (32). A solution of **30** (730 mg, 2.0 mmol), 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (6.89 mg, 4.0 mmol), and hydroquinone (2-3 mg) in CH_3CN (12 mL) was degassed and sealed in an ampule that was then heated to 75 °C for 2 h. This solution was diluted with $CHCl_3$, washed with 1.0 N aqueous HCl (3 × 50 mL), H_2O (1 × 50 mL), and brine (2 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated to give 1.59 g of a brown oil. This was treated with CF_3CO_2H for 20 min at room temperature, and the solution was then poured into 150 mL of 5% aqueous $NaHCO_3$ and ice. This was diluted with $CHCl_3$ (300 mL), washed with 5% aqueous $NaHCO_3$ (3 × 50 mL), H_2O (1 × 50 mL), and brine (2 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated to give a brown tar that was flash chromatographed on silica gel to yield 857 mg (92%) of a yellow solid. Recrystallization from acetone/chloroform gave a white material that proved to be the methoxy-ketone addition product, with a 3:1 mixture of stereoisomers at position C(6).

A small sample of the major stereoisomer was separated and purified by low pressure chromatography on silica gel (EtOAc/Et_2O/petroleum ether, 2:1:2), then crystallized from acetone: mp 171.5–173 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 8.36 (m, 1 H, H-aromatic), 7.85 (m, 3 H, H-aromatic), 5.77 (s, H-C(8)), 4.55 (d, J = 7.0, H-C(1)), 3.84 (dd, J = 12.0, 6.5, H-C(6)), 3.33 (dd, J = 6.0, 2.0, H-C(2)), 3.19 (s, 3 H, OCH_3), 3.01 (dd, J = 14.0, 7.0, H_{exo}-C(10)), 2.94 (dd, J = 16.0, 6.0, H-C(3)), 2.79 (dd, J = 19.0, 6.5, H-C(5)), 2.63 (dd, J = 19.0, 12.0, H-C(5)), 2.61 (d, J = 16.0, H-C(3)), 2.41 (d, J = 14.0, H_{endo}-C(10)), 2.15 (s, 3 H, CH_3).

Minor isomer: ^1H NMR (360 MHz, $CDCl_3$) δ 8.24 (m, 1 H, H-aromatic), 7.81 (m, 2 H, H-aromatic), 7.74 (m, 1 H, H-aromatic), 5.34 (s, H-C(8)), 4.55 (d, J = 7.0, H-C(1)), 4.23 (dd, J = 9.5, 5.0, H-C(6)), 3.34 (dd, J = 8.0, 7.0, H-C(2)), 3.15 (br s, 3 H, OCH_3), 3.07 (dd, J = 16.0, 7.0, H-C(3)), 3.01 (ddd, J = 13.5, 7.0, 0.75, H_{exo}-C(10)), 2.60 (dd, J = 19.5, 5.0, H-C(5)), 2.52 (d, J = 13.5, H_{endo}-C(10)), 2.33 (dd, J = 16.0, 8.0, H-C(3)), 2.15 (s, 3 H, CH_3), 1.83 (ddm, J = 19.5, 9.5, H-C(5)).

5-Benzenesulfonyl-7-oxabicyclo[2.2.1]hept-5-en-2-one (33a). A solution of **12** (3.82 g, 34.7 mmol) and phenylselenenyl phenylsulfone (12.9 g, 43.4 mmol) in benzene (300 mL) was bubbled with a stream of N_2 gas and stirred at 20 °C while being irradiated with a 125-W high pressure Hg arc lamp. The light was filtered through a solution of $BiCl_3$ (0.0045 M in 10% aqueous HCl, cutoff at 355 nm). After 3 h the solution was concentrated to a yellow solution (ca. 50 mL), ether was added, and a crude white solid was filtered from solution. The filtrate was concentrated in a similar manner and treated as above to give a second portion of this material that was combined with the first to give 8.68 g (61%) of crude product. This did not prove ammenable to purification by either chromatography or crystallization and was therefore oxidized directly in the next step. ^1H NMR (360 MHz, $CDCl_3$): 7.26–7.97 (m, 10 H, H-aromatic), 5.37 (d, J = 6.25, H-C(4)), 4.34 (d, J = 5.75, H-C(1)), 3.92 (dd, J = 5.75, 5.5, H-C(6)), 3.23 (d, J = 5.5, H-C(5)), 2.63 (dd, J = 17.5, 6.25, H_{exo}-C(3)), 1.99 (d, J = 17.5, H_{endo}-C(3)).

A portion of this solid (4.80 g), as a solution in CH_2Cl_2 (500 mL), was stirred under a dry N_2 atmosphere at −65 to −70 °C while a solution of *m*-CPBA (1.97 g, 11.4 mm, 2.19 g of 90%) in CH_2Cl_2 (250 mL) was added dropwise over 1.5 h. Stirring at this temperature was continued for an additional 3 h, and then the solution was warmed slowly over 5 h to room temperature and stirred overnight. The resulting yellow solution was washed with 5% aqueous $Na_2S_2O_5$ (2 × 50 mL), 5% aqueous $NaHCO_3$ (3 × 50 mL), and brine (1 × 50 mL) and then was dried ($MgSO_4$), filtered, and concentrated to give 5.05 g of a yellow oily solid. Flash chromatography gave 1.87 g of a pale yellow solid, **33a**, containing a trace of the lactone resulting from overoxidation. Crystallization from EtOAc/petroleum ether (1:1) gave 1.48 g (53%, 32% from **12**) of analytically pure material: mp 109.5–110.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.96 (m, 2 H, H-aromatic), 7.74 (m, 1 H, H-aromatic), 7.65 (m, 2 H, H-aromatic), 7.07 (dm, J = 2.0, H-C(6)), 5.36 (dm, J = 4.5, H-C(4)), 4.80 (m, H-C(1)), 2.34 (dd, J = 16.5, 4.5, H_{exo}-C(3)), 1.94 (d, J = 16.5, H_{endo}-C(3)).

(1*RS*,2*SR*,7*RS*,8*RS*)-7-Benzenesulfonyl-11-oxatricyclo-[6.2.1.$0^{2,7}$]undec-5-ene-4,10-dione (37). A solution of **33a** (250 mg, 1.0 mmol), 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (344 mg, 2.0 mmol), and hydroquinone (2–3 mg) in toluene (2 mL) was heated in a closed flask under a nitrogen atmosphere at 80 °C for 2 h. Toluene (5 mL) was added and the solution was then cooled to 0 °C before adding $BF_3{\cdot}Et_2O$ (282 mg, 2.0 mm). The solution was stirred at 0 °C for 30 min and then poured into a mixture of 5% aqueous $NaHCO_3$ (50 mL) and ice. To this mixture was added $CHCl_3$ (100 mL), and then, after separating the phases, the organic solution was washed with 5% aqueous $NaHCO_3$ (3 × 25 mL) and brine (1 × 25 mL) before being dried ($MgSO_4$), filtered, and concentrated to give 605 mg of a brown oil. Analysis of the crude product by ^1H NMR indicated the ratio of the desired enone **33a** to the β-methoxy ketone **36** to be about 2.1. Flash chromatography of this material on silica gel (EtOAc/Et_2O/$CHCl_3$) gave 134 mg of a yellow oil, which was crystallized from EtOAc/petroleum ether (1:1) to yield 80 mg of **37**: mp 186–188 °C dec; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (m, 2 H, H-aromatic), 7.75 (m, 1 H, H-aromatic), 7.63 (m, 2 H, H-aromatic), 6.91 (dd, J = 10.25, 0.75, H-C(6)), 6.14 (d, J = 10.25, H-C(5)), 4.89 (dd, J = 6.0, 1.5, H-C(8)), 4.26 (br s, H-C(1)), 3.60 (d, J = 18.5, H_{endo}-C(9)), 3.36 (br d, J = 8.5, H-C(2)), 2.77 (ddd, J = 18.5, 6.0, 1.5, H_{exo}-C(9)), 2.45 (br d, J = 17.0, Hs-C(3)), 2.08 (dd, J = 17.0, 8.5, Hr-C(3)).

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Registry No. (±)-**11**, 84120-97-8; (±)-**12**, 94482-73-2; (±)-**13a**, 105183-21-9; (±)-**13b**, 105183-22-0; (±)-**13c**, 105183-23-1; (±)-**14**, 105183-24-2; (±)-**14b**, 105183-25-3; (±)-**14c**, 105183-26-4; (±)-**15**, 105183-27-5; (±)-**16**, 105183-28-6; (±)-**17**, 105183-29-7; (±)-**18**, 105183-30-0; (±)-**19**, 105228-47-5; (±)-**20**, 105183-31-1; (±)-**21**, 105228-48-6; **22**, 59414-23-2; (±)-**23**, 105183-32-2; (±)-**23** (spiro), 105183-38-8; (±)-**24**, 105183-33-3; **25**, 33285-87-9; **26**, 1226-72-8; **26** (diol), 582-17-2; (±)-**29**, 105183-34-4; (±)-**30**, 105183-35-5; **31**, 105205-35-4; (±)-**32** (isomer 1), 105183-36-6; (±)-**32** (isomer 2),

105183-36-6; (±)-**33a**, 105183-37-7; (±)-**34**, 105205-34-3; PhSeCl, 931-59-9; 2-$O_2NC_6H_4SO_2Cl$, 7669-54-7; $PhSeSO_2Ph$, 60805-71-2; 1,3-cyclopentadiene, 542-92-7; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7.

Supplementary Material Available: UV, IR, ^{13}C NMR, and MS spectral data and elemental analyses of all new compounds (9 pages). Ordering information is given on any current masthead page.

"Naked Sugars" as Synthetic Intermediates. Total Synthesis of L-Daunosamine[1]

Aleksander Warm and Pierre Vogel*

Institut de chimie organique de l'Université, CH-1005 Lausanne, Switzerland

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The "naked sugars" are optically pure synthetic intermediates. Their advantage compared with natural sugars is that they possess a number of unsubstituted carbon atoms that can be substituted stereospecifically through direct procedures. (1*S*,2*R*,4*S*)-2-[(−)-Camphanoyloxy]-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile ((+)-1) is an example of a "naked sugar". Electrophilic reagents add to the C(5),C(6) double bond, giving the corresponding adducts where the electrophile substitutes the exo position of C(6) and the nucleophile the endo position at C(5). This principle was used to prepare (1*R*,4*R*,5*R*)-5-*endo*-chloro-7-oxa-2-bicyclo[2.2.1]heptanone (**13**), which was monomethylated stereoselectively in the exo position at C(3), giving (+)-(1*R*,3*S*,4*R*,5*R*)-5-*endo*-chloro-3-*exo*-methyl-7-oxa-2-bicyclo[2.2.1]heptanone (**14**). The latter was transformed stereospecifically into L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose). The (−)-camphanic acid used to engender asymmetry was recovered at an early stage of the synthesis.

Derivatives of 7-oxabicyclo[2.2.1]heptane have been used as starting materials in the synthesis of anthracyclines,[2] nucleosides,[3] muscarine derivatives,[4] prostaglandins,[5] cyclitols derivatives,[6] and other material of biological interest.[7] Some derivatives have also been shown to exhibit antitumor[8] or antiinflammatory activity.[9] We recently reported the preparation of the two optically pure 7-oxabicyclo[2.2.1]hept-5-enes, (+)-1 and (+)-**2**.[10,11] These systems can be seen as "naked sugars" since positions C(3), C(5), and C(6) can be functionalized in a stereospecific fashion by direct procedures, without protection and/or deprotection steps. In the preceding paper[12] we showed that the regioselectivity of the highly stereoselective electrophilic additions of the C(5)–C(6) double bond depends upon the nature of the substituents at C(2). We shall see here that 7-oxa-2-bicyclo[2.2.1]heptanone derivatives can be monoalkylated stereoselectivity at position C(3). Thus, like natural sugars, the naked sugars (+)-1 and (+)-**2** are optically pure molecules; their advantage compared with sugars is that they are already "defoliated" and ready to undergo modifications of the carbon skeleton in a stereoselective, if not stereospecific, fashion. This principle is now illustrated by the total synthesis of L-daunosamine **3** (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose).[13] This important amino sugar is the carbohydrate component of antitumor anthracycline antibiotics such as Adriamycin and Daunomycin.[14] Several ingenious syntheses of **3** have been reported starting from carbohydrate[15] and nonsugar substrates.[16] The technology de-

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