$J = 8$ Hz); exact mass calcd for $C_{16}H_{20}NO_2Cl$ m/e 293.1182, found m/e 293.1171.

(±)-(1α,4aα,9aβ)-1,3,4,9a-Tetrahydro-2-methyl-8-methoxy-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine [(±)-10·HCl]. A solution of (±)-9·HCl (560 mg, 1.70 mmol) in 20% aqueous acetic acid (30 mL) was hydrogenated over 10% Pd/C (100 mg) at 45 psi for 20 h. The catalyst was removed by filtration and the filtrate evaporated to a white solid. Crystallization (THF/MeOH) gave (±)-10·HCl as a white solid (471 mg, 94%): mp 234–237 °C; CIMS, m/e 260 (MH^+); NMR δ 1.45–2.32 (m, 7 H), 2.54 (s, 3 H), 2.84–3.18 (m, 3 H), 3.41–3.52 (m, 1 H), 3.91 (s, 3 H), 4.23 (d, 1 H, $J = 3$ Hz), 6.93–6.70 (m, 3 H).

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl \cdot CH_3OH$: C, 62.28; H, 7.99; N, 4.27. Found: C, 62.03; H, 8.08; N, 4.02.

(±)-(1α,4aα,9aβ)-1,3,4,9a-Tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol [(±)-3·HCl]. A solution of (±)-10·HCl (400 mg, 1.36 mmol) in $CHCl_3$ (30 mL) was stirred at 20 °C while BBr_3 (800 μL, 8.5 mmol) was slowly added. A colorless oil was rapidly deposited on the flask wall. After 20 min the mixture was shaken with 5% aqueous NH_4OH (10 mL) and the $CHCl_3$ layer removed and combined with a $CHCl_3$ extract (10 mL) of the residual aqueous layer. Drying (Na_2SO_4) and evaporation of solvent yielded a foam (393 mg), which was acidified with methanolic HCl, evaporated, and crystallized (THF/MeOH) as a white hydrochloride salt, yielding (±)-3·HCl (280 mg, 73%): mp 278–280 °C; CIMS (CH_4), m/e 246 (MH^+); NMR (free base) δ 1.48–2.25 (m, 7 H), 2.58 (s, 3 H), 2.91–3.07 (m, 2 H), 3.45 (t, 0.5 H, $J = 6.5$ Hz), 3.57–3.65 (m, 1 H), 3.69 (t, 0.5 H, $J = 6.5$ Hz), 4.03 (d, 1 H, $J = 3$ Hz), 6.58 (dd, 1 H, $J = 3$ Hz, 5 Hz), 6.66–6.75 (m, 2 H).

Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.19; H, 7.88; N, 5.48.

Crystallographic data for (±)-3: $C_{15}H_{19}NO_2$, M_r 245.32; space group = $Pbc2_1$; radiation = Cu K_α (graphite monochromator); wavelength = 1.5418 Å; cell dimensions, $a = 6.947$ (1) Å, $b = 12.896$ (1) Å, $c = 14.115$ (1) Å; $V = 1264.5$ Å^3; $D_x = 1.29$ g/cm^3; $Z = 4$; $\sin\theta/\lambda$ (max) = 0.6221 Å^{-1}; 1337 reflections (190 with $I < \sigma(I)$); function minimized, $\sum \omega \Delta^2$; $R = 0.032$.

The phase problem was solved by the use of programs of MULTAN78.[7] The model was refined by using the programs of XRAY72,[8] and all hydrogen atoms were visible in a difference map. The final R factor, using anisotropic thermal parameters, exp$(-2\pi^2(\sum_i \sum_j U_{ij} a_i^* a_j^* h_i h_j))$ for the heavier atoms and isotropic parameters for the H atoms, was 3.2%. The atomic parameters and the bond angles are included in the supplementary material, and calculated structure factors were submitted to the referees and may be obtained from J.V.S.

Acknowledgment. We thank Mr. Noel Whittaker for chemical-ionization mass spectra, Mr. William Landis for electron-impact ionization mass spectra, and Mrs. Paula Parisius and Alice Wong for combustion analysis.

Registry No. (±)-3, 90171-26-9; (±)-3·HCl, 90243-04-2; (±)-4, 88304-31-8; (±)-5, 90149-45-4; (±)-6, 90149-46-5; (±)-7, 90149-47-6; (±)-8, 90149-48-7; (±)-9, 90149-49-8; (±)-9·HCl, 90242-11-8; (±)-10·HCl, 90149-50-1.

Supplementary Material Available: Tables of atomic parameters for the heavier atoms and bond angles (3 pages). Ordering information is given on any current masthead page.

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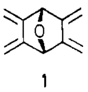
Communications

2,5-Bis[[(*Z*)-(2-nitrophenyl)sulfenyl]methylene]-3,6-dimethylene-7-oxabicyclo[2.2.1]heptane. A Versatile Reagent for Tandem Regioselective Diels–Alder Reactions

Summary: The title compound may be used to generate polyfunctional, multicyclic molecules with high regio- and stereoselectivity via two successive Diels–Alder additions using two different dienophiles.

Sir: The 2,3,5,6-tetramethylene-7-oxabicyclo[2.2.1]heptane (1), readily obtained from the inexpensive furan and maleic anhydride,[1] can be used to prepare various anthracycline precursors.[2,3] The principle of our strategy rests upon the fact that the rate constant for the Diels–Alder addition of 1 is much larger than that for the reaction of the corresponding monoadduct with the same dienophile.[4] The utility of this synthesis principle[5] would be highly enhanced if the regioselectivity of the two successive or "tandem"[6,7] cycloadditions could be controlled. This is possible through stereospecific substitution of the two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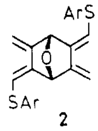

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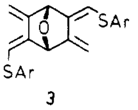

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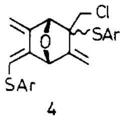

4

Ar = $2\text{-}NO_2C_6H_4$

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(4) For possible explanations of this phenomenom, see: Pilet, P.; Vogel, P. *Helv. Chim. Acta* **1981**, *64*, 2563. Pilet, O.; Birbaum, J.-L.; Vogel, P. *Ibid.* **1983**, *66*, 19.

(5) It has been called a "doubly, doubly convergent" synthesis; see: Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801 and references cited therein.

(6) This term has been used recently by Trost and Shimizu[7] for classifiying the 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene which allows the generation of two rings in two successive cycloadditions. One should notice that the two diene moieties in 1 and 2 are generated in the same synthetic step whereas for Trost's reagent, two different synthetic steps are required to generate the two diene moieties.

(7) Trost, B. M.; Shimizu, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 4299. See also: Trost, B. M.; Remuson, R. *Tetrahedron Lett.* **1983**, *24*, 1129 and the "timed Diels–Alder reactions"; Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974.

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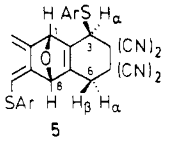
diene moieties in 1 by groups capable of controlling the regioselectivity of the Diels–Alder additions.[8] We report results that manifest this principle.

Double addition of 2-nitrobenzenesulfenyl chloride (2.25 molar equiv, AcOH, 8–9% LiCl, 20 °C, 3 h) to 1 gave a mixture of bisadducts from which the major isomer precipited (60–70%), but due to its instability, the stereochemistry of the addition has yet to be established. Double elimination of HCl (3 molar equiv of *t*-BuOK, THF, –78 to 20 °C) yielded the symmetrical, disubstituted tetraene 2 (mp 187–188 °C, 80%, isolated) whose structure was given by two-dimensional NMR spectroscopy (δ_H vs. δ_C) and NOE measurements in the ^{1}H NMR spectrum (CDCl$_3$, δ 8.25–7.34 (m, 8 H), 6.49 (s, 2 H), 5.67 (br s, 2 H), 5.45 (s, 2 H), 5.37 (s 2 H)). The bisadducts left in the mother liquor from the sulfenylation reaction gave a mixture of 2 (major), 3, and 4 when treated with *t*-BuOK in THF. The evident high regioselectivity in the sulfenylation of 1 could be due either to kinetic control, in the addition, or to preferential stabilization of one bisadduct (by crystallization). The double HCl elimination is also highly stereoselective.

The Diels–Alder additions to exocyclic dienes grafted onto 7-oxabicyclo[2.2.1]heptanes are generally exo face selective,[9] and this is the case for the addition of ethylenetetracarbonitrile to 2 acetone (50 °C, 14 h), which yielded the monoadduct 5 (mp 207–208 °C, 81%). However, the cycloaddition of butynone to 2 in benzene (50 °C, 40 h) yielded uniquely 6 (mp 132–133 °C, 84%), the product resulting from endo face attack. Similarly, the reactions of 2 with methyl vinyl ketone (benzene, 100 °C, 2.5 h) was endo face selective, giving a 9:1 mixture (95%) of monoadducts 7 (mp 208–209 °C) and 8 (mp 130–131 °C), which were readily separated by column chromatography on silica gel. Interestingly, this latter addition was highly stereoselective with respect to the acetyl side chain in 7 and 8. Analogous selectivities were observed for the reaction of 2 with methyl acrylate (neat, 70 °C, 15 h) which gave a 4:1 mixture (94%) of 9 (mp 188–189 °C) and 10 (mp 180–181 °C). As expected,[10] the additions of 2 were highly "ortho" regioselective; no trace of corresponding "meta" adducts could be detected. As in the case of 1, the formation of bisadducts of 2 was found to be at least 50 times slower than the first dienophile addition. The monoadducts can thus be isolated in good yield and used directly in a second cycloaddition with another dienophile. For example, when 7 was heated with an excess of methyl propynoate (benzene, 80 °C, 72 h), adduct 11 was formed which eliminated 1 equiv of 2-nitrobenzenesulfenic acid under the conditions of its formation, yielding 12 (mp 190–191 °C, 70%). The addition of methyl vinyl ketone (BF$_3$·Et$_2$O, CH$_2$Cl$_2$, –78 °C, 120 h) to 9 gave 13 (70%) together with an unidentified product (4%) arising probably from double bond isomerizations.



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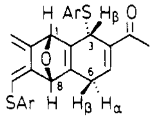

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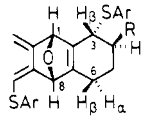
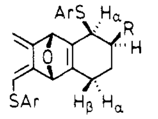
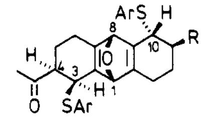




R = COCH$_3$: 7 8

R = COOCH$_3$: 9 10

11 12



13

R=COOCH$_3$

The structures of adducts 5–13 were deduced from their spectral data. The relative configurations of the ArS groups were given by the long-range homoallylic coupling constants between the bridgehead protons and the proton adjacent to the sulfenyl substituent.[9a,11] If the latter is in the β-position, i.e., syn to the oxa bridge, a value of $^5J_{H,H}$ = 1–1.8 Hz is expected, whereas $^5J_{H,H}$ should be <0.2 Hz for a proton in the α-position (e.g., $^5J_{H\text{-}3,H\text{-}8}$ = 1.8 Hz in 6, 1.0 Hz in 7, but <0.2 Hz in 5, 8, and 13). The relative configurations of the acetyl or/and ester side chains in 7–13 was given by the other $J_{H,H}$ coupling constants. They will be confirmed by X-ray analysis.

Two successive Diels–Alder additions to tetraene 2 offers easy access to polyfunctional, multicyclic molecules in which the various substituents can be introduced stereo- and regioselectively. Applications of this principle to the synthesis of natural products are currently being explored in our laboratory.

Acknowledgment. We thank Hoffmann-La Roche & Co., AG, Basel, the Swiss National Science Foundation, and the Fonds Herbette, Lausanne, for generous support.

Registry No. 1, 53011-99-7; 2, 90413-90-4; 3, 90413-91-5; 4, 90432-17-0; 5, 90413-92-6; 6, 90432-18-1; 7, 90413-93-7; 8, 90458-31-4; 9, 90413-94-8; 10, 90458-32-5; 11, 90413-95-9; 12, 90413-96-0; 13, 90413-97-1; ethylenetetracarbonitrile, 670-54-2; butynone, 1423-60-5; methyl vinyl ketone, 78-94-4; methyl propynoate, 922-67-8; 2-nitrobenzenesulfenyl chloride, 7669-54-7.

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