(2S,4R,6R)-Trimethyloctanoic acid: ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 2.60 (m, 1 H).

Acknowledgment. We thank Professor Mario Silva and his students for their assistance in obtaining samples of the siphonariid. The research was funded by grants from the National Science Foundation (CHE-8121471) and the National Institutes of Health (PHS-11969).

Registry No. 4, 90220-12-5; 5, 90220-13-6.

Probes for Narcotic Receptor Mediated Phenomena. 6.[1] Synthesis of (±)-(1α,4aα,9aβ)-1,3,4,9a-Tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol, an Oxide-Bridged 5-(3-Hydroxyphenyl)morphan

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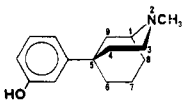
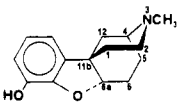
In our continuing study of the opioid receptor system,[1] we have examined conformationally fixed derivatives of the potent class of narcotic agonists, the 5-(3-hydroxyphenyl)morphans **1**.[2] The parent compounds have a rigid 2-azabicyclo[3.3.1]nonane ring system with a freely rotating phenyl group attached at the 5-position. An unusual feature of this system is that the phenyl ring is held in an equatorial conformation relative to the fixed piperidine portion of the molecule, which consists of atoms 1–5 and 9 of structure **1**. This is in contrast to the axial phenyl–piperidine orientation found in the opiates and a number of rigid opioids.



1



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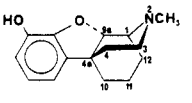


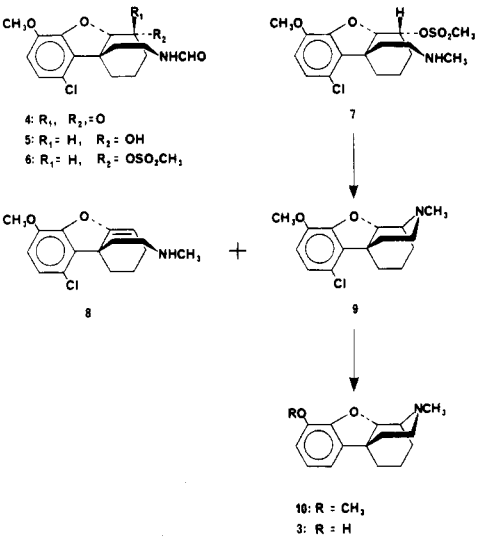
3

In order to gain additional insight into the topological features of opioid receptor binding sites, we have undertaken a study aimed at determining the optimum torsion angle between the phenyl ring and piperidine ring for binding of the 5-(3-hydroxyphenyl)morphan nucleus to an opioid receptor. The approach that we have taken is to conformationally restrict rotation of the phenyl ring by means of an oxide bridge to one of three carbons, 4, 6, or 9 of **1**. Since each carbon offers two epimeric sites of attachment, a total of six oxide bridge isomers are possible, each having the phenyl ring rotated at an angle of approximately 60° relative to the previous isomer in the series. The six isomers together sequentially rotate the phenyl ring through a complete 360° revolution. Should any of these isomers bind well to an opioid receptor, valuable information about the optimum phenyl–piperidine torsion angle would be obtained.

The first isomer in this series, **2**, has been synthesized and the torsion angle between the phenyl ring and the piperidine ring (the plane of the piperidine ring was calculated as a least-squares plane through atoms 1, 2, 4, and 12 of **2**) was calculated as 86° on the basis of X-ray analysis of **2**·HCl.[3] The inability of **2** to bind to opioid receptor preparations[4] might be related to the unsuitable phenyl torsion angle. This paper presents the synthesis of the second isomer in the series, racemic **3**, and the determination of its phenyl torsion angle by X-ray analysis. This synthesis of **3** represents the first entry into the 2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine series.

Synthesis

The synthesis of **3** started with hexahydrodibenzofuran **4**,[3] which was obtained by using the heteroatom-directed photoarylation developed by Schultz[5] and previously employed by us as an intermediate in the synthesis of **2**. To form the tetrahydropropanobenzofuro[2,3-*c*]pyridine ring system of **3** it was necessary to effect ring closure of the nitrogen onto the carbonyl carbon atom of **4**. Attempts



at closure by nucleophilic attack of nitrogen at the carbonyl carbon proved unsuccessful. A less direct route involved reduction of the carbonyl function with $NaBH_4$ to yield predominately one alcohol **5** which was assigned the α-configuration on the basis of the 3-Hz coupling constant for the 4aβ proton of **5**. As in the case of the 6aβ proton of **2**, the low-field absorption of the 4aβ proton of **5** is attributed to the deshielding effect of the aromatic ring.[3] Crystallization of the crude mixture gave pure **5** in 69% yield. Conversion of **5** to the corresponding methanesulfonate ester **6** was achieved in 90% yield by reaction of **5** with methanesulfonyl chloride in the presence of triethylamine. The *N*-formyl group was reduced with diborane to yield the secondary amine **7**. It was anticipated that intramolecular displacement of the methanesulfonate group by nitrogen would occur cleanly to give the desired ring-closed product **9**.

However, in addition to **9** obtained in 18% yield from **7**, a byproduct was also obtained in 9% yield which pro-

(1) For paper 5 in this series, see: Jacobson, A. E.; Bajwa, B. S.; Streaty; R. A.; Klee, W. A.; Rice, K. C. *Life Sci.* **1983**, *33* (*Suppl. I*), 159.
(2) May, E. L.; Murphy, J. G. *J. Org. Chem.* **1954**, *19*, 618.
(3) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 1051.
(4) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weismann, B. A.; Silverton, J. V. *Prob. Drug Depend.*, in press.
(5) Schultz, A. G.; Motyka, L. A. In "Organic Photochemistry"; Padwa, A., ed.; Marcel Dekker: New York, 1983; Vol. 6, p 1.

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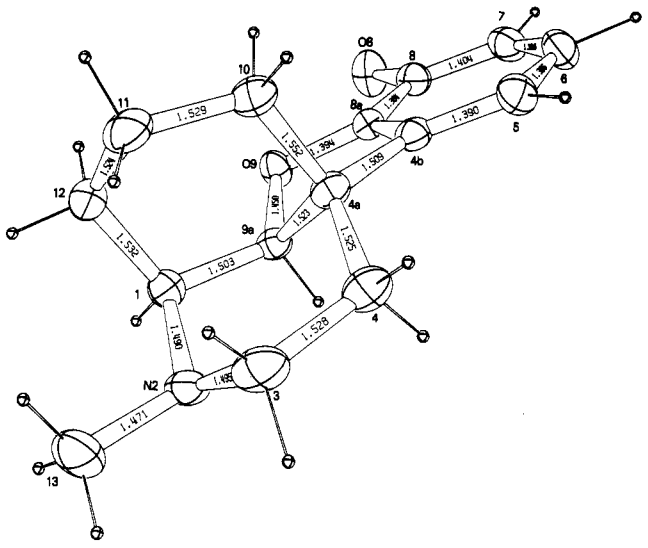

Figure 1. ORTEP[9] drawing of (±)-3 showing crystal conformation and bond lengths.

vided spectral data consistent with structure 8. Examination of Dreiding models of 7 indicated unstrained six-membered rings between both nitrogen and C(4) that allow intramolecular displacement leading to product 9 and between nitrogen and the H(4aβ) leading to the elimination product 8. The synthesis was completed by hydrogenolysis of the C(5)-chlorine of 9 with 10% Pd/C to yield 10 in 94% yield and demethylation of 10 with BBr_3 to give 3 in 73% yield.[6]

Conclusion

X-ray structure analysis of (±)-3 confirmed the structure and indicated that the phenyl ring was held at an angle of 8° with respect to a least-squares plane through atoms 1, 3, 4, and 9a of the piperidine ring. The crystal conformation and bond lengths are shown in Figure 1. The molecular strain in 3 as indicated by Dreiding models is corroborated by the molecular dimensions, particularly the bond angles. The angle C(4)–C(4a)–C(9a) is unusually small (97.9°) and C(4a)–C(4b)–C(5) is unusually large (133.4°), and several other angles involving formally sp^3 hybridized atoms deviate considerably from the tetrahedral angle. In the crystal, intermolecular distances correspond to van der Waals interactions except for a hydrogen bond between O(8) and N(2) along the twofold screw axis, which appears to be the controlling factor in the packing (O(8)···N(2) 2.72 Å and H(8)···N(2) 1.75 Å).

The biological activity of (±)-3 has previously been reported.[4] Although it binds only weakly to opioid receptor preparations from rat brain homogenate (EC_{50} = 96 nM for (±)-3 as compared to EC_{50} = 5.2 nM for (+)-1 and 9.6 nM for (−)-1), its binding is 18-fold greater then for the oxide bridge isomer (±)-2 (EC_{50} = 1766 nM).[4] This may indicate that the torsion angle of 8° in (±)-3 is approaching that required for optimum binding to the receptor. Synthesis of the remaining four isomers in the series should provide a definitive statement of the phenyl–piperidine torsion angle needed for maximum binding.

Experimental Section

Melting points were determined on a Fischer-Johns apparatus and are corrected. NMR spectra were recorded with a Varian 220-MHz spectrometer with $(CH_3)_4Si$ as the internal reference and $CDCl_3$ as the solvent. IR spectra were recorded on a Beckman IR 4230 spectrometer. Chemical-ionization mass spectra were obtained on a Finnigan 1015D spectrometer with a Model 6000 data collection system and electron-ionization mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Column chromatography was performed with use of 230–400-mesh EM silica gel. Both mass spectra and elemental analyses were obtained from the Section on Analytical Services and Instrumentation, NIADDK.

(±)-4aα-Hydroxy-6-methoxy-9-chloro-9bβ-[2-(formylamino)ethyl]-1,2,3,4,4aβ,9b-hexahydrodibenzofuran [(±)-5]. A suspension of (±)-4[3] (5.0 g, 15 mmol) in MeOH (50 mL) was stirred at 3 °C while $NaBH_4$ (588 mg, 15 mmol) was added. After 30 min, the solvent was evaporated and the resulting foam partitioned between H_2O (50 mL) and $CHCl_3$ (2 × 100 mL). Drying ($MgSO_4$) and evaporation of solvent gave a syrup, which after dilution with a small volume of MeOH was crystallized from ether to yield analytically pure (±)-5 as white crystals (3.44 g, 69%): mp 157–160 °C; CIMS (CH_4), m/e 325, 327 (MH^+); NMR δ 1.39–2.02 (m, 6 H), 2.27–2.50 (m, 2 H), 2.98–3.27 (m, 1 H), 3.34–3.54 (m, 1 H), 3.84 (s, 3 H), 3.89–4.02 (m, 1 H), 4.73 (d, 1 H, J = 3 Hz), 5.73 (s, 1 H), 6.68 (d, 1 H, J = 8 Hz), 6.77 (d, 1 H, J = 8 Hz), 8.09 (s, 1 H).

Anal. Calcd for $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; N, 4.30. Found: C, 58.88; H, 6.06; N, 4.16.

(±)-4aα-[(Methylsulfonyl)oxy]-6-methoxy-9-chloro-9bβ-[2-(formylamino)ethyl]-1,2,3,4,4aβ,9b-hexahydrodibenzofuran [(±)-6]. A solution of (±)-5 (3.44 g, 10.6 mmol) and methanesulfonyl chloride (4.4 g, 39.0 mmol) in $CHCl_3$ (100 mL) was stirred at 20 °C while triethylamine (6 mL) was added. After 10 min the reaction mixture was diluted with $CHCl_3$ (100 mL), washed with 1 N HCl (100 mL), dried ($MgSO_4$), and evaporated. Crystallization (ether/MeOH) gave analytically pure (±)-6 as a white solid (3.86 g, 90% yield): mp 142–146 °C; CIMS (CH_4), m/e 403, 405 (MH^+); NMR δ 1.48–2.09 (m, 6 H), 2.32–2.50 (m, 2 H), 2.95–3.23 (m, 1 H), 3.14 (s, 3 H), 3.86 (s, 3 H), 4.86 (d, 1 H, J = 3 Hz), 4.95–5.07 (m, 1 H), 5.68 (s, 1 H), 6.70 (d, 1 H, J = 8 Hz), 6.80 (d, 1 H, J = 8 Hz), 8.09 (s, 1 H).

Anal. Calcd for $C_{17}H_{22}ClNO_6S \cdot {}^1/_2CH_3OH$: C, 50.06; H, 5.76; N, 3.34. Found: C, 49.89; H, 5.50; N 3.33.

(±)-4α-[(Methylsulfonyl)oxy]-6-methoxy-9-chloro-9bβ-[2-(methylamino)ethyl]-1,2,3,4,4aβ,9b-hexahydrodibenzofuran [(±)-7]. A solution of (±)-6 (3.40 g, 8.4 mmol) in dry THF (120 mL) was stirred for 3 h at 72 °C with BH_3 (20 mL of 1.0 M in THF). Excess hydride was destroyed by stirring an additional 15 min with MeOH (10 mL) and then the mixture was evaporated to a foam. The foam was taken up in MeOH (100 mL) and stirred for 15 min at 72 °C with 37% HCl (1 mL). Solvent was evaporated and the residue partitioned between saturated aqueous $NaHCO_3$ (100 mL) and $CHCl_3$ (2 × 100 mL), dried (Na_2SO_4), and evaporated, yielding crude (±)-7 as a yellow syrup (3.7 g) of sufficient purity for further use: EIMS, m/e 389, 391 (M^+); NMR δ 1.32–2.09 (m, 6 H), 2,23–2.66 (m, 4 H), 2.39 (s, 3 H), 3.08 (s, 3 H), 3.86 (s, 3 H), 4.84 (d, 1 H, J = 3 Hz), 4.98–5.09 (m, 1 H), 6.70 (d, 1 H, J = 8 Hz), 6.77 (d, 1 H, J = 8 Hz).

(±)-(1α,4aα,9aβ)-1,3,4,9a-Tetrahydro-2-methyl-8-methoxy-5-chloro-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine [(±)-9·HCl]. A solution of (±)-7 (3.5 g, 9.0 mmol) in DMF (50 mL) was stired at 100 °C with powdered $KHCO_3$ (6.3 g, 63 mmol). After 30 min additional DMF (25 mL) was added to break up the gel-like mass. At the end of 24 h the mixture was cooled, filtered, and evaporated. The resulting brown residue was partitioned between H_2O (50 mL) and $CHCl_3$ (2 × 100 mL) and dried (Na_2SO_4) and the $CHCl_3$ extract evaporated to a foam (2.91 g). Silica gel flash chromatography (EtOAc/MeOH, 1:1) yielded elimination product 8 (220 mg) and the desired ring-closure product (±)-9 (783 mg). Crystallization of (±)-9·HCl from THF gave white crystals (564 mg, 18%): mp 230–233 °C; CIMS (NH_3), m/e 294, 296 (MH^+); NMR (free base) δ 1.87–2.33 (m, 6 H), 2.53 (s, 3 H), 2.59 (dd, 1 H, J = 6 Hz, 12 Hz), 2.77–3.11 (m, 3 H), 3.30–3.41 (m, 1 H), 3.86 (s, 3 H), 4.20 (d, 1 H, J = 3 Hz), 6.66 (d, 1 H, J = 3 Hz), 6.75 (d, 1 H, J = 8 Hz); exact mass calcd for $C_{16}H_{20}NO_2Cl$ m/e 293.1182, found m/e 293.1191.

Anal. Calcd for $C_{16}H_{20}ClNO_2 \cdot HCl \cdot {}^1/_4H_2O$: C, 57.41; H, 6.47; N, 4.18. Found: C, 57.13; H, 6.05; N, 4.03.

For side-product 8: CIMS (NH_3), m/e 294, 296 (MH^+); NMR δ 1.61–2.27 (m, 9 H), 2.32 (s, 3 H), 2.66–2.68 (m, 2 H), 3.89 (s, 3 H), 5.29 (t, 1 H, J = 4 Hz), 6.73 (d, 1 H, J = 8 Hz), 6.84 (d, 1 H,

(6) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.

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 $C_{16}H_{21}NO_2$·HCl·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 $C_{15}H_{19}NO_2$·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 θ/λ (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($-2\pi^2(\sum_i\sum_j U_{ij}a_i^*a_j^*h_ih_j)$) 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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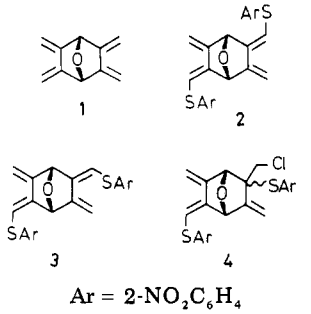
Communications

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



1 2 3 4

Ar = 2-$NO_2C_6H_4$

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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(3) Tamariz, J.; Schwager, L.; Stibbard, J. H. A.; Vogel, P. *Tetrahedron Lett.* **1983**, *24*, 1497. Tamariz, J.; Vogel, P. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 74.

(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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