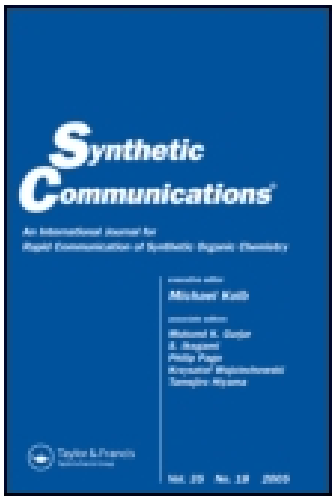

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

NEW SYNTHETIC ROUTE TO C_2-SYMMETRIC 2,2′-BIPYRIDINES: SYNTHESIS OF (6R,6′R,8R,8′R)-6,8,6′,8′-BISMETHANO-7,7,7′,7′-TETRA-METHYL-5,5′,6,6′,7,7′,8,8′-OCTAHYDRO- 2,2′-BIQUINOLINE

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Published online: 16 Aug 2006.

To cite this article: Giorgio Chelucci & Antonio Saba (2001) NEW SYNTHETIC ROUTE TO C_2-SYMMETRIC 2,2′-BIPYRIDINES: SYNTHESIS OF (6R,6′R,8R,8′R)-6,8,6′, 8′-BISMETHANO-7,7,7′,7′-TETRA- METHYL-5,5′,6,6′,7,7′,8,8′-OCTAHYDRO-2,2′-BIQUINOLINE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:20, 3161-3166, DOI: 10.1081/SCC-100105892

To link to this article: http://dx.doi.org/10.1081/SCC-100105892

SYNTHETIC COMMUNICATIONS, 31(20), 3161–3166 (2001)

NEW SYNTHETIC ROUTE TO C_2-SYMMETRIC 2,2′-BIPYRIDINES: SYNTHESIS OF (6R,6′R,8R,8′R)-6,8,6′,8′-BISMETHANO-7,7,7′,7′-TETRAMETHYL-5,5′,6,6′,7,7′,8,8′-OCTAHYDRO-2,2′-BIQUINOLINE

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ABSTRACT

A generalizable procedure to C_2-symmetric 2,2′-bipyridines based on two consecutive constructions of the pyridine rings is reported. As an example of this strategy the title bipyridine has been prepared in four steps from 3-benzyloxy-2-butanone and (1R,5R)-3-methylenenopinone.

Chiral derivatives of 2,2′-bipyridines and in particular those provided of C_2-symmetry are finding increased utility as auxiliaries for metal catalyzed asymmetric catalysis.[1,2] Notwithstanding this, relatively few chiral C_2-symmetric bipyridine ligands has been reported and used in asymmetric

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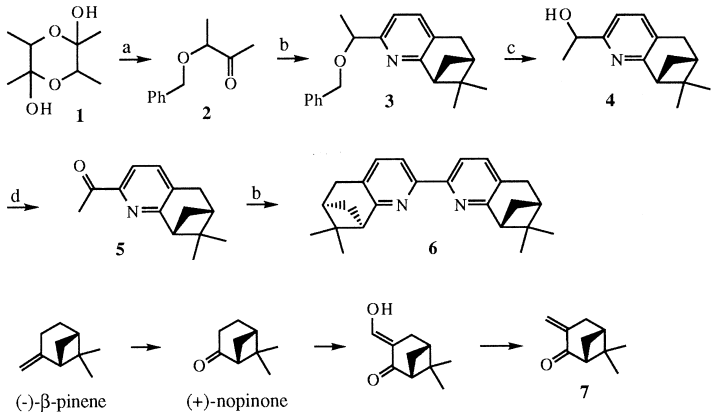
catalysis.[3] One reason associated with this problem is the lack of efficient and alternative synthetic routes to them. In fact, the nickel-mediated homocoupling of 2-halopyridines is the sole method reported so far.[2]

The difficulties associated with the preparation of 2-halopyridines have led us to explore new procedures for obtaining such ligands. Here we describe a generalizable procedure for the preparation of C_2-symmetric bipyridines, specifically, the synthesis of the pinano-fused bipyridine **6**[4] from (+)-nopinone which was selected as a prototype from which to develop the basic methodology.

The synthesis of 2,2′-bipyridine **6** began with racemic 3-benzyloxy-2-butanone **2** which was prepared from the dimeric ketal **1** by heating under reflux a mixture of benzyl alcohol and concentrated hydrochloric acid in toluene on a Dean-Stark apparatus[5] (Scheme 1). Then, the pyridine **3** was obtained by conjugate addition of the lithium enolate of the benzylketone **2** with (1R,5R)-3-methylenenopinone (**7**), in turn obtained from (-)-β-pinene[6] (Scheme 1, at the bottom), followed by azaanellation of unisolated 1,5-dicarbonyl intermediate with the ammonium acetate/acetic acid system (23% overall yield). Catalytic hydrogenolysis of the benzyl derivative **3** (Pd/C at 3 atm.) gave the carbinol **4** (92%) which was oxidized under the condition of Swern reaction to ketone **5** (93%). Starting from this key intermediate, the bipyridine **6** was prepared by building up the second pyridine ring in a similar way to that used to prepare **3** from **2** (35% overall yield).



a: $PhCH_2OH$, toluene, conc. HCl; b: LDA, THF, -40 °C, 2 h then **7**; then $MeCOONH_4$, MeCOOH; c: H_2, Pd/C, MeOH, 3 atm; d: Swern oxidation;

Scheme 1.

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In conclusion, the present protocol to C_2-symmetric bipyridines offers an useful alternative to the method based on the homocoupling of 2-halopyridines.

EXPERIMENTAL SECTION

Boiling points are uncorrected. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The ^{1}H-NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Chemical shifts are reported in ppm downfield from internal Me_4Si. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyser. Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$ under argon. 3-Hydroxy-2-butanone dimer and lithium diisopropylamine (LDA, 2M solution in heptane/THF/ethylbenzene) were purchased from Aldrich Chemical Co. (1R,5R)-3-Methylenenopinone (**7**) was prepared from (-)-β-pinene (99% pure, Aldrich) according to a reported procedure.[6]

3-(Phenylmethoxy)-2-butanone (2): A solution of 1 (17.1 g, 0.1 mol) and benzyl alcohol (32.4 g, 0.3 mol) in toluene (40 ml) containing concentrated hydrochloric acid (10 ml) was refluxed for 45 min on a Dean-Stark apparatus. Then the toluene was evaporated and the oily residue was distilled in vacuo to give 2 (10.5 g, 59%): bp_2 110°C; ^{1}H-NMR ($CDCl_3$) δ: 7.38–7.29 (m, 5H), 4.56 (d, 1H, $J = 11.7$ Hz), 4.49 (d, 1H, $J = 11.7$ Hz), 3.90 (q, 1H, $J = 6.8$ Hz), 2.20 (s, 3H), 1.34 (d, 3H, J = 7.1). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 9.92. Found: C, 74.25; H, 9.97.

(6R,8R)-6,8-Methano-7,7-dimethyl-2-[(1-phenylmethoxy)ethyl]-5,6,7,8-tetrahydroquinoline (3): A solution of **2** (8.16 g, 46 mmol) in anhydrous THF (5 ml) was added dropwise at −78°C to a solution of lithium diisopropylamine (46 mmol) in anhydrous THF (230 ml) under an argon atmosphere. The resulting solution was stirred at −40°C for 2 h and then a solution of 3-methylenenopinone (**7**) (6.9 g, 46 mmol) in THF (20 ml) was added dropwise at −40°C. After 15 min at −40°C, the solution was allowed to reach slowly room temperature and then poured into a mixture of ammonium acetate (71 g, 50 mmol) and acetic acid (230 ml). The flask was connected with a distillation head and the THF was distilled off over a 3-h period. Most part of the acetic acid was removed under reduced pressure and the residue taken up with H_2O and extracted with ethyl ether. The organic phase was separated and extracted with a 10% HCl solution. The acid solution was neutralized with a 5% NaOH solution and extracted with ethyl ether. The organic phase was dried on anhydrous Na_2SO_4, the solvent

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was evaporated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 9/1) to give **3** as a mixture of diastereomers (in a ratio 6/4): 3.25 g (23%); oil; ^{1}H-NMR ($CDCl_3$); major isomer, δ: 7.43 (d, 1H, J = 7.8), 7.37–7.22 (m, 6H), 4.59 (m, 1H), 4.46 (m, 2H), 2.97 (m, 1H), 2.93 (s, 2H), 2.33 (m, 1H), 1.50 (d, 3H, J = 6.6 Hz), 1.42 (s, 3H), 1.31 (d, 1H, J = 9.6 Hz), 0.66 (s, 3H). Minor isomer, δ: 7.43 (d, 1H, J = 7.8), 7.37–7.22 (m, 6H), 4.59 (m, 1H), 4.46 (m, 2H), 2.97 (m, 1H), 2.93 (s, 2H), 2.33 (m, 1H), 1.51 (d, 3H, J = 6.6 Hz), 1.42 (s, 3H), 1.30 (d, 1H, J = 9.6 Hz), 0.67 (s, 3H). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.03; H, 8.20; N, 4.56. Found: C, 82.15; H, 8.06; N, 4.66.

(6R,8R)-2-[(1-hydroxy)ethyl]-6,8-methano-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (4): A mixture of **3** (3.07 g, 10 mol), 10% palladium on carbon in 95% ethanol (40 ml) was hydrogenated at room temperature and 3 atm in a Parr apparatus. Hydrogen absorption ceased after the uptake of one equivalent of Hydrogen. The mixture was filtered and the filtrate evaporated at reduced pressure to give an oil. Purification of this oil by chromatography on SiO_2 (petroleum ether/ethyl acetate = 7/3) gave **4** as a mixture of diastereomers (in a ratio 6/4) (2.0 g, 92%): oil;^{1}H-NMR ($CDCl_3$); major isomer, δ: 7.40 (d, 1H, J = 7.5), 7.04 (d, 1H, J = 7.5 Hz), 4.82 (q, 1H, J = 6.6 Hz), 4.65 (s broad, 1H), 2.98 (t, 1H, J = 5.7 Hz), 2.92 (d, 2H, J = 2.4 Hz), 2.70 (m, 1H), 2.33 (m, 1H), 1.48 (d, 3H, J = 6.6 Hz), 1.42 (s, 3H), 1.28 (d, 1H, J = 9.6), 0.64 (s, 3H). Minor isomer, δ: 7.40 (d, 1H, J = 7.5), 7.02 (d, 1H, J = 7.5 Hz), 4.82 (q, 1H, J = 6.6 Hz), 4.65 (s broad, 1H), 2.98 (t, 1H, J = 5.7 Hz), 2.92 (d, 2H, J = 2.4 Hz), 2.70 (m, 1H), 2.33 (m, 1H), 1.48 (d, 3H, J = 6.6 Hz), 1.42 (s, 3H), 1.27 (d, 1H, J = 9.6 Hz), 0.65 (s, 3H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.82; N, 6.45. Found: C, 77.55; H, 8.92; N, 6.33.

(6R,8R)-(−)-2-ethanoyl-6,8-methano-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (5): A solution of dimethyl sulfoxide (0.82 g, 10.5 mmol) in anhydrous CH_2Cl_2 (3 ml) was added dropwise to a solution of oxalyl chloride (0.66 g, 5.3 mmol) in CH_2Cl_2 (13 ml) at −60°C. After stirring for 5 min a solution of 4 (0.87 g, 4 mmol) in CH_2Cl_2 (5 ml) was added. The cloudy mixture was stirred at −60°C for 50 min and Et_3N (2.03 g, 20 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 1 h. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic phase was dried on anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 7/3) to give **5**: 0.8 g (93%); oil; $[\alpha]_D^{25}$-20.2. (*c* 2.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.85 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.8 Hz), 3.06 (t, 1H, J = 5.7 Hz), 3.00 (d, 2H, J = 2.7 Hz), 2.76 (m, 1H), 2.69 (s, 3H), 2.35 (m, 1H), 1.44 (s, 3H), 1.29 (d, 1H, J = 9.6 Hz), 0.66 (s, 3H). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.09; H, 7.96; N, 6.51. Found: C, 78.23; H, 7.84; N, 6.61.

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(6R,6′R,8R,8′R)-(+)-6,8,6′,8′-Bismethano-7,7,7′,7′-tetramethyl-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-biquinoline (6): Following the procedure used for the preparation of **3** and starting from 5 (0.78 g, 36 mmol) a crude mixture was obtained (1 g). Purification of this mixture by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 9/1) gave **6** (436 mg, 35%): mp 163–164°C; $[\alpha]_D^{25}$+41.3 (*c* 1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 8.07 (d, 2H, J = 8.1 Hz), 7.50 (d, 2H, J = 8.1 Hz), 3.10 (t, 2H, J = 5.7 Hz), 2.97 (d, 4H, J = 2.7 Hz), 2.74 (m, 2H), 2.33 (m, 2H), 1.42 (s, 6H), 1.35 (d, 2H, J = 9.6 Hz), 0.67(s, 6H). Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.67; H, 8.20; N, 8.14. Found: C, 83.77; H, 8.29; N, 8.05.

ACKNOWLEDGMENT

Thanks are due to Mr. Mauro Mucedda for experimental assistance. Financial support by M.U.R.S.T. and by Regione Autonoma Sardegna is gratefully acknowledged.

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Received in the Netherlands January 2, 2001

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