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Novel Synthesis of 1,6,7,9-Tetrasubstituted 8-Oxo-1-azaspiro[4.4]nonanes

David Gravestock* and Jean M. McKenzie#

School of Chemical and Physical Sciences, University of Natal, Pietermaritzburg, Private Bag X01, Scottsville, 3209 South Africa.

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ABSTRACT

The synthesis and isolation of one diastereomer of 1-benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile 11 **was accomplished by the diiron nonacarbonyl-assisted spirocyclization reaction of 2-(1-benzyl-2-pyrrolidinylidene)acetonitrile** 10 **and 2,4-dibromo-3-pentanone** 12. **NOESY NMR spectroscopy experiments of** 11 **showed it to be the (5*R**,6*S**,7*S**,9*S**)-diastereomer.**

KEYWORDS

Iron-mediated [2+3] cycloaddition reactions, α,α′-dibromoketones, vinylogous cyanamides, 1-azaspiro[4.4]nonanes, diiron nonacarbonyl.

The stereochemical and functional diversity contained in natural products such as cephalotaxine **1**[1,2] (Fig. 1) possessing 1-azaspirocyclic ring structures[3] has resulted in the development of numerous strategies[4] for the synthesis of the azaspirocyclic systems which constitute the structural core of these alkaloids.

Reported in this communication are some preliminary findings concerning a method of producing highly functionalized 8-oxo-1-azaspiro[4.4]nonanes. The recent Nobel laureate Noyori and his co-workers developed an iron-mediated [3 + 2] cycloaddition reaction between α,α′-dibromoketones **2** and alkenes **3** for the preparation of functionalized cyclopentanones **4** as shown in Scheme 1.[5,6]

At the outset of the project we wished to investigate whether 2-methylenepyrrolidines **5** could be coupled to α,α′-dibromo ketones **6** in the presence of $Fe_2(CO)_9$ to form 8-oxo-1-azaspiro[4.4]nonanes **7** (Scheme 2). 2,4-Dibromo-3-pentanone **6** (R′ = Me) was the dibromoketone of choice, as the Noyori annulation reaction does not work with α,α′-dibromoacetone **6** (R′ = H). Noyori reasoned that inductively-donating alkyl groups are required in order to stabilize the cationic reactive intermediates. 2,4-Dibromo-3-pentanone is thus the simplest symmetrical α,α′-dibromoketone that we could have chosen for our model study. We chose an alkene **5** bearing a benzyl group on nitrogen as it seemed the simplest analogue of the more complex substituent bonded to the nitrogen atom in cephalotaxine **1**. In principle, we should be able to remove the benzyl group at a later stage by catalytic hydrogenation and replace it with a group of our choice.

Vinylogous cyanamide **10** was synthesized in a two-step process from 1-benzylpyrrolidin-2-one **8**[7] (Scheme 3). The first step involved the conversion of **8** into the corresponding thiolactam **9**,[7d,8] which was achieved by the method of Brillon (54%).[8] Our NMR spectroscopic data were in good agreement with those of Brillon.[8] The synthesis of the vinylogous cyanamide **10** was achieved using an Eschenmoser coupling reaction between thiolactam **9** and bromoacetonitrile (75%).[9,10] This appears to be a novel compound, and it was exhaustively characterized using HRMS, IR and NMR spectroscopy. The ^{13}C NMR spectrum of the vinylogous cyanamide **10** was particularly valuable for its characterization. Two quaternary signals (δ_C 114.53 and 165.82) were assigned to the nitrile carbon and the carbon β to the nitrile group respectively, and a methine signal (δ_C 54.46) was assigned to the carbon α to the nitrile group.

The reaction between vinylogous cyanamide **10**, 2,4-dibromo-3-pentanone **12** and $Fe_2(CO)_9$ was carried out by heating the reaction mixture for 18 h with concomitant irradiation (Scheme 3).[11] It proved impossible to purify the crude reaction mixture by radial chromatography. NMR spectra were obtained on the

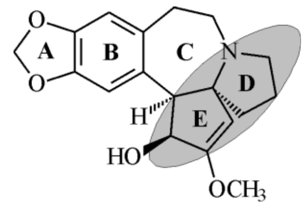

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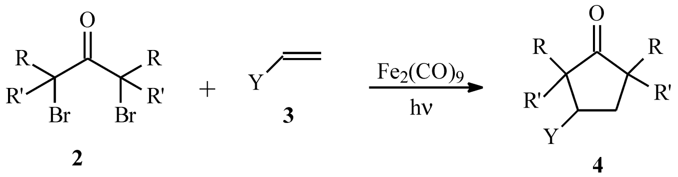
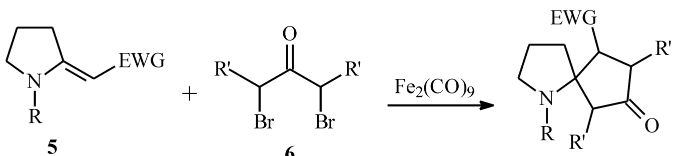
Figure 1 Structure of cephalotaxine 1. The 1-azaspiro[4.4]nonane core is highlighted.



2 **3** **4**

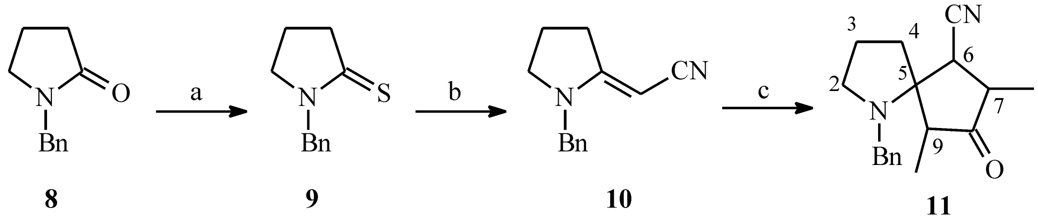
Scheme 1
R, R′ = alkyl, aryl; Y = alkyl, aryl, NR_2.



5 **6** **7**

Scheme 2
EWG = CN, COR, CO_2R, NO_2; R, R′ = alkyl, aryl.

* To whom correspondence should be addressed; Fax: +27 (33) 260 5009; E-mail: gravestockd@nu.ac.za. # Present address: Department of Chemistry, University of Stellenbosch, Private Bag X1, 7602 Matieland, South Africa



Scheme 3

Reagents and conditions: (a) P_4S_{10}, Na_2CO_3, THF, rt, 54%; (b) $BrCH_2CN$, CH_3CN, rt then Et_3N, Ph_3P, rt, 75%; (c) 2,4-dibromo-3-pentanone **12**, $Fe_2(CO)_9$, benzene, h*v*, 50°C.

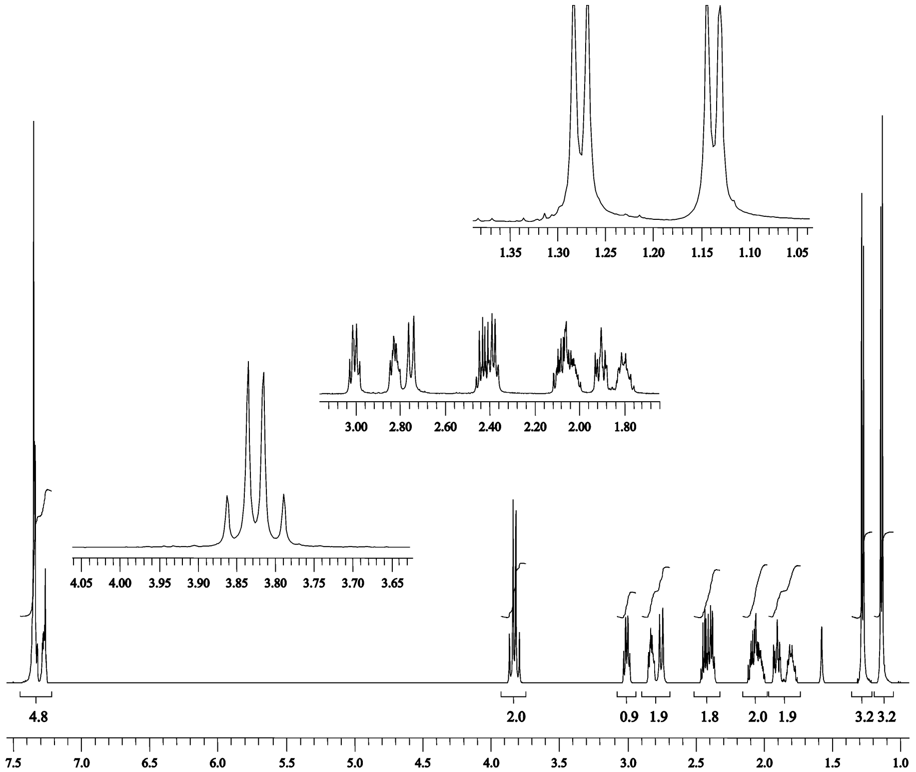


Figure 2 500 MHz ^{1}H NMR spectrum of (±)-(5*R**,6*S**,7*S**,9*S**)-1-benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile **11** and expansions of the regions *ca.* δ 1.1–1.4, *ca.* δ 1.8–3.1 and *ca.* δ 3.7–3.9.

partially separated fractions and it was clear to see that the desired product had been formed, as it was possible to identify the presence of the key features of the molecule such as the phenyl ring, methyl groups, nitrile carbon and carbonyl carbon atoms. Perhaps the most important peak observed in the ^{13}C NMR spectra was the quaternary carbon at the spiro-fused centre that appeared in the region δ_C 70–75. Fortuitously, one of the compounds crystallized out selectively, and the signals in both its ^{1}H and ^{13}C NMR spectra could be unambiguously identified as belonging to (±)-(5*R**,6*S**,7*S**,9*S**)-1-benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile **11** with the help of DEPT, COSY, GHSQC and GHMQC spectra. The ^{1}H NMR spectrum obtained for this novel azaspirocycle is shown in Fig. 2, and the assignments were made as follows. The two methyl peaks α to the carbonyl group both appear as doublets as expected, with the methyl groups attached to C-9 and C-7 resonating at δ 1.14 and δ 1.27, respectively. All the methylene protons on the pyrrolidine ring are diastereotopic; one C-3 proton occurs 1.80–1.85, while the other forms part of the multiplet at δ 1.99–2.11. One C-4 proton appears at δ 1.88–1.93 with the other being part of the δ 1.99–2.11 multiplet. The last pyrrolidine methylene group at C-2 has one diastereotopic proton appearing at δ 2.80–2.84 and the other at δ 2.98–3.03. The methine protons on C-9 and C-7 appear together as a multiplet at δ 2.36–2.46, while the C*H* which is α to the nitrile group is clearly seen as a doublet at δ 2.75. The benzyl CH_2 protons are also diastereotopic, each resonating as a doublet at δ 3.81 and 3.84. The peak at approximately δ 1.60 is a minor impurity.

NOESY experiments were carried out on the crystalline diastereomer in an attempt to establish the relative stereochemistry for the four stereogenic centres (Fig. 3). Irradiation of the methyl group attached to C-9 showed a through-space correlation to the methine proton at C-7, indicating a *trans* relationship between the two methyl groups. The *trans* relationship of the methyl groups was confirmed by irradiation of the methyl group attached to C-7, as this showed a correlation to the C-9 proton. This C-7 methyl group also showed a correlation to the C-6 proton α to the nitrile group, indicating a *trans* relationship

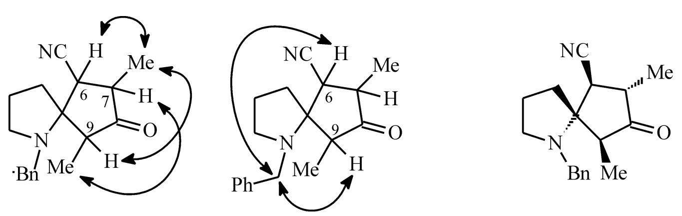


Figure 3 NOEs observed and the relative stereochemistry proposed for azaspirocycle **11**.

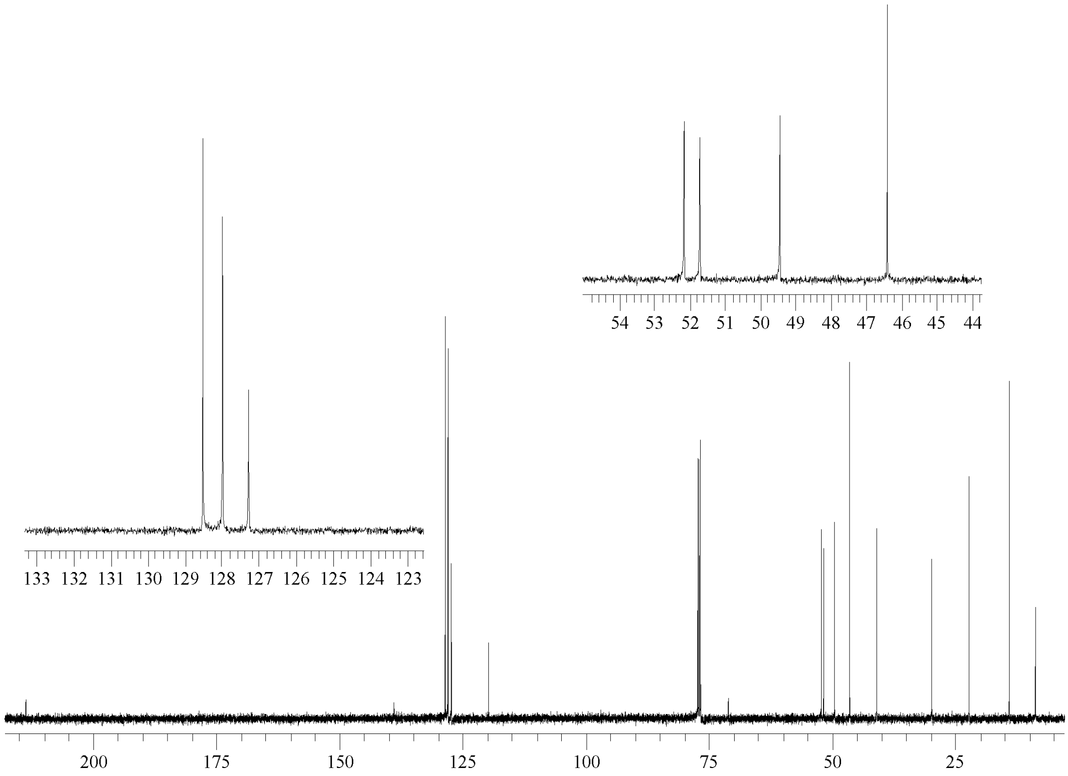


Figure 4 125 MHz ^{13}C NMR spectrum of (±)-(5*R**,6*S**,7*S**,9*S**)-1-benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile **11** and expansions of the regions *ca.* δ 44–54 and *ca.* δ 123–133.

between the methyl group attached to C-7 and the nitrile group. Finally, irradiation of the benzyl CH_2 protons showed a correlation to both the C-9 and C-6 protons. The C-9 and C-6 protons both appeared to be *cis* to one another from the observations described above, and thus if the benzyl group shows a correlation to both these protons, the ring nitrogen must also be *cis* to them. Based on the above NOESY experimental data the relative stereochemistry of azaspirocycle **11** was predicted to be 5*R**,6*S**,7*S**,9*S** as shown in Fig. 3.

The ^{13}C NMR spectrum for the spirocycle **11** is shown in Fig. 4. The quaternary spiro-fused carbon atom resonates at δ 71.08. Other obvious signals are those for the two methyl groups (δ 8.70 and 14.06), the nitrile carbon (δ 119.69) and the carbonyl carbon (δ 213.71).

An X-ray crystal structure was obtained on compound **11**.[12] The X-ray crystal structure confirmed that the relative stereochemistry of the crystalline diastereomer of azaspirocycle **11** was indeed 5*R**,6*S**,7*S**,9*S** as predicted in Fig. 3 from the NOESY results.

In conclusion, it can be seen that a highly functionalized 8-oxo-1-azaspiro[4.4]nonane can be synthesized in a few simple steps from relatively inexpensive starting materials. Using higher homologues of lactam **8** should in turn lead to the formation of 3-oxo-6-azaspiro[4.5]decane and the 3-oxo-6-azaspiro [4.6]undecane ring systems. Studies testing these potential extensions as well as the ability of the spirocyclization reaction to tolerate a variety of substituents on the α,α′-dibromoketone and a variety of electron-withdrawing groups on the enamine are the subject matter for future studies.

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10 Bromoacetonitrile (0.60 cm^3, 8.67 mmol) was added to 1-benzylpyrrolidine-2-thione **9** (1.10 g, 5.75 mmol) in acetonitrile (5 cm^3) and the resulting mixture was left to stir for 18 h at room temperature. Triphenylphosphine (2.26 g, 8.63 mmol) and dry triethylamine (1.20 cm^3, 8.63 mmol) were mixed in dichloromethane (5 cm^3) and this solution was added to the reaction mixture and left to stir for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 cm^3) and the aqueous layer was extracted with EtOAc (3 × 15 cm^3). The combined organic portions were dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo.* The remaining oil was dissolved in a CH_2Cl_2/hexane mixture (50%, 50 cm^3) and cooled to precipitate the triphenylphosphine sulfide by-product, which was filtered off. The solids were washed with a cold CH_2Cl_2/hexane mixture (50%). This procedure was repeated, the solvent was evaporated *in vacuo* and the residue was purified by radial chromatography (CH_2Cl_2-hexane 50%) to afford *2-(1-benzyl-2-pyrrolidinylidene)acetonitrile* **10** as a yellow oil (853 mg, 75%); R_f 0.36 (CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 7.16–7.36 (5H, m, arom H), 4.28 (2H, s, CH_2Ar), 3.58 (1H, s, NC=C*H*), 3.42 (2H, t, *J* 6.9, NCH_2CH_2), 2.94 (2H, t, *J* 7.7, =CCH_2) and 2.01 (2H, quintet, *J* 7.3, $CH_2CH_2CH_2$); δ_C (125 MHz, $CDCl_3$) 165.82 (N*C*=CH), 135.33 (Ar C-1′), 128.86, 127.77, 127.17 (Ar C-2′, C-3′, C-4′), 114.53 (C≡N), 54.46 (C=CHCN), 53.62 (NCH_2CH_2), 50.08 (CH_2Ar), 32.75 (=CCH_2) and 20.81 ($CH_2CH_2CH_2$); v_{max}/cm^{-1} (film) 3100–2860 (CH), 2248 (C≡N), 1617 (C=C) and 1082 (C-N); *m/z* (EI) 198 (37%, M^+), 92 (8), 91 (100, CH_2Ar) and 65 (11) (Found: M^+, 198.1152. $C_{13}H_{14}N_2$ requires 198.1157).

11 2-(1-Benzyl-2-pyrrolidinylidene)acetonitrile **10** (0.85 g, 4.3 mmol) dissolved in benzene (10–15 cm^3) and 2,4-dibromo-3-pentanone **12** (1.57 g, 6.44 mmol, passed through a basic alumina column before use) dissolved in benzene (10–15 cm^3) were added to $Fe_2(CO)_9$ (1.49 g, 4.10 mmol). The resulting mixture was stirred overnight under N_2 at 50°C with irradiation from a 400 W high pressure Hg lamp [used with an aqueous $CuSO_4$ solution (10% w/v) functioning as a filter to block wavelengths of less than 350 nm]. The solution was diluted with EtOAc (30 cm^3) and then washed with saturated aqueous $NaHCO_3$ (40 cm^3) followed by a brine solution (40 cm^3). The organic layer was separated and dried ($MgSO_4$), filtered and the solvent removed under vacuum. Attempts to purify the mixture of products using radial chromatography (10% EtOAc/hexane) were unsuccessful. *(5R*,6S*,7S*,9S*)-1-Benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile* **11** selectively crystallized out from an EtOAc/hexane solution to give large, colourless crystals; R_f 0.49 (EtOAc-hexane, 20%); m.p. 108.5–110.5°C; δ_H (500 MHz; $CDCl_3$) 7.25–7.35 (5H, m, arom H), 3.84 (1H, d, *J* 13.3, ArC$H_a$$H_b$), 3.81 (1H, d, *J* 13.3, ArC$H_a$$H_b$), 2.98–3.03 (1H, m, NC$H_aH_bCH_2$), 2.80–2.84 (1H, m, NC$H_aH_bCH_2$), 2.75 (1H, d, *J* 11.4, C*H*C≡N), 2.36–2.46 (2H, m, 2 × MeC*H*), 1.99–2.11 (2H, m, $CH_2CH_aH_bCH_2$ and NCCH_aH_b), 1.88–1.93 (1H, m, NCCH_aH_b), 1.75–1.85 (1H, m, $CH_2CH_aH_bCH_2$), 1.27 (3H, d, *J* 7.3, CHCH*Me*) and 1.14 (3H, d, *J* 6.9, CCH*Me*); δ_C (125 MHz; $CDCl_3$) 213.71 (*C*=O), 138.94 (Ar C-1′), 128.52, 127.99, 127.29 (Ar C-2′, C-3′, C-4′), 119.69 (C≡N), 71.08 (*C*-N), 52.17 (NCH_2CH_2), 51.72 (CH_2Ar), 49.44 (CCHMe), 46.40 (CHCHMe), 40.88 (*C*HC≡N), 29.76 (NCCH_2), 22.16 ($CH_2CH_2CH_2$), 14.06 (CHCH*Me*) and 8.70 (CCH*Me*); v_{max}/cm^{-1} (KBr disc) 3100–2800 (CH), 2237 (C≡N), 1747 (C=O) and 1076 (C-N); *m/z* (EI) 282 (18%, M^+), 200 (13), 188 (14), 187 (100), 186 (28) and 91 (71, CH_2Ar) (Found: M^+, 282.1734. $C_{18}H_{22}N_2O$ requires 282.1732).

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