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Synthetic studies on morphine-based analgesics: an approach to angular substitution in 4a-aryldecahydroisoquinolines via dienolate chemistry

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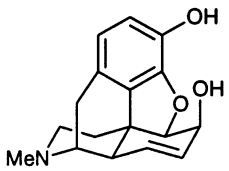
Abstract—The reaction of the dienolate generated from **9** using lithium hexamethyldisilazide with a range of alkyl halides has been explored and the regioselectivity and stereochemistry of the adducts determined. Reaction of the dienolate with an oxaziridine gave hydroxylation at the C-8a position as found in some potent morphine-like analgesics.

The search for non-addictive opiate analgesics based on the morphine structure **1** has occupied organic chemists for many years. Out of this work has come a variety of substructures of morphine such as the morphinan skeleton **2**,[1] the benzomorphan skeleton **3**[2] and more recently the *trans*-4a-aryldecahydroisoquinoline skeleton **4**.[3] These ring systems provide a basic scaffold on which chemists can introduce functionality to provide receptor selectivity (μ, δ and κ receptors) and agonist/antagonist properties.[4] A particularly interesting site at which to introduce functionality is the angular position within the hydroisoquinoline ring.[5] Thus, dihydrooxymorphone **5** carrying an angular hydroxyl group is a more potent analgesic than morphine but with lower physical dependence side effects. Naloxone **6** is a pure antagonist while the closely related nalorphine **7**, lacking the angular hydroxyl group, is a partial agonist. The angular substituent need not be a hydroxyl group. The presence of an angular alkyl group leads to compound **8** which is a considerably more potent analgesic than morphine.[6] However, the introduction of such functionality is not synthetically trivial. A recent publication[7] reporting the introduction of an angular (8a) hydroxyl group into the *trans*-4a-aryldecahydroisoquinoline skeleton prompts us to report our results directed towards the introduction of both alkyl and hydroxy functionality at this position.



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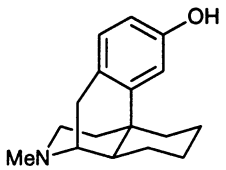

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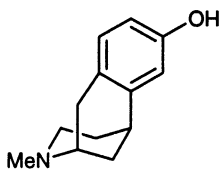

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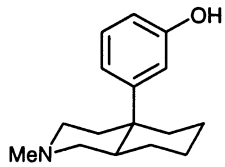

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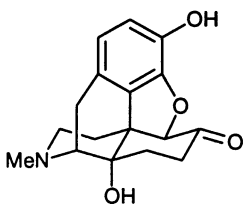

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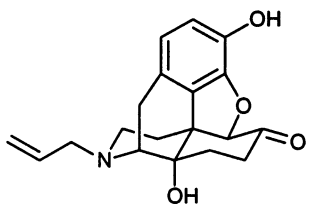

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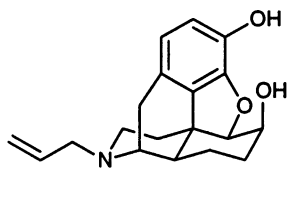

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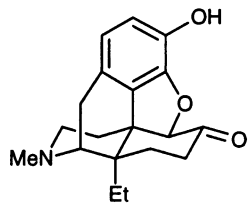

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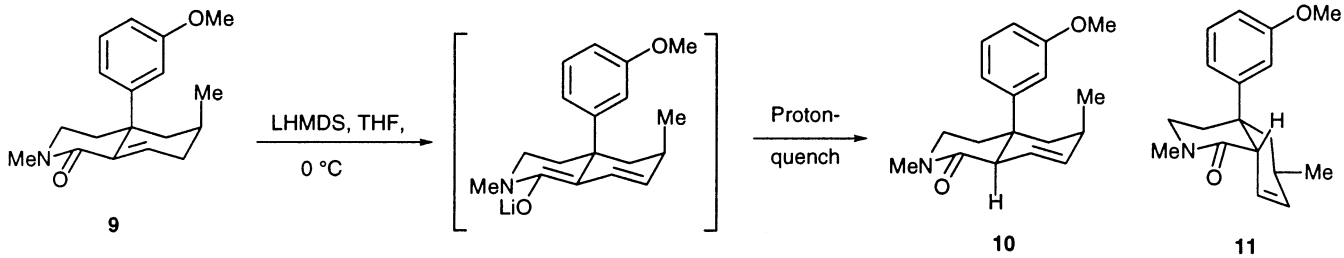
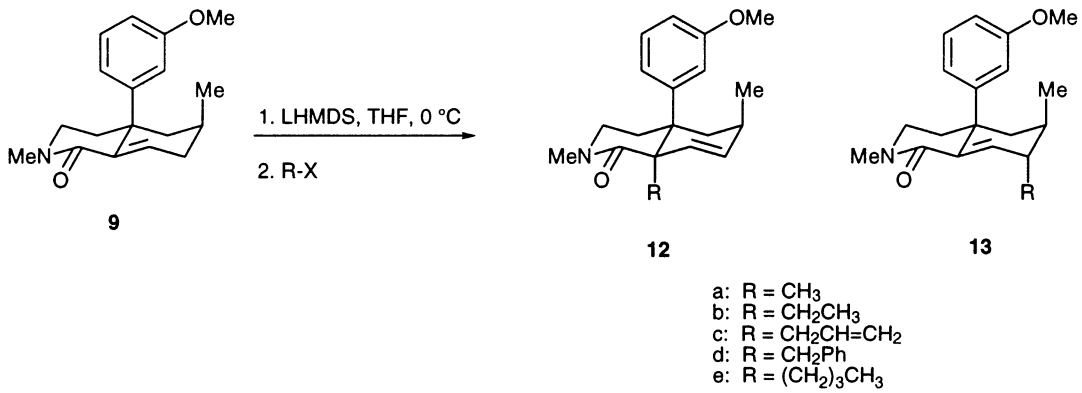


Scheme 1.



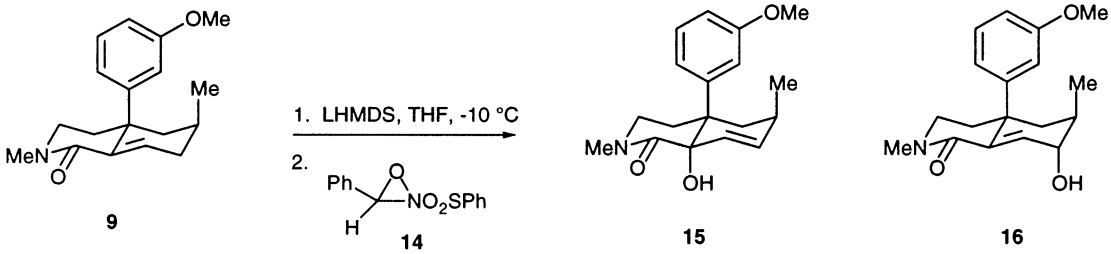
Scheme 2.

We have reported a convenient synthesis of the 4a-aryloctahydroisoquinolone **9** in ca. 20% overall yield from 3-methoxyacetophenone via an intramolecular Diels–Alder reaction.[3] Furthermore, formation of the dienolate using lithium hexamethyldisilazide (LHMDS) followed by quenching with a proton source gave rise to two β,γ-unsaturated lactams **10** and **11** (Scheme 1), which can be readily distinguished by the chemical shift of the methyl group in the ^{1}H NMR. The *trans*-ring junction in **10** forces the methyl group into the face of the aromatic ring leading to a significant upfield shift. Depending upon the quenching agent, **10** could be isolated in some 70% yield. We felt that generation of the dienolate from **9** and reaction with other electrophiles could lead to introduction of a variety of functionality at the angular position.

The factors affecting the regioselectivity of reactions of dienolates derived from α,β-unsaturated carboxylic acids with electrophiles have been extensively explored.[8] However, little work has been published concerning amide and lactam dienolates, although the seminal paper of Snieckus showed that the α- versus γ-reactivity is dependent on the metal counterion.[9] More recently, asymmetric α-alkylation has been reported with good control of both the absolute stereochemistry of the new stereogenic centre and the double bond geometry.[10] In line with the results of Snieckus, we decided to use a lithium amide base for the generation of the dienolate of **9** in order to favour α-reactivity. Treatment of **9** with LHMDS at 0°C gave an orange-coloured solution of the dienolate which was reacted with a range of alkylating agents. Reaction with a slight excess of methyl iodide (Table 1, entry 1) gave a 9:1 mixture (by NMR) of the α-alkylated product **12a** and the γ-alkylated product **13a** in 58% yield. The major product, **12a**, was isolated from the product mixture in 52% yield but the minor product, **13a**, could not be isolated in a pure form and its structure was assigned on the basis of NMR spectra of the mixture and by analogy with subsequent products. The presence of the C-7/C-8 double bond in **12a** was apparent from the proton NMR (resonances at δ 5.35 and 6.40 each integrating for 1H). The stereochemistry of **12a** was readily determined by the unusual upfield shift of the C-6 methyl group in the proton NMR (δ 0.28), which clearly indicated a *trans*-ring junction.[3] As expected, alkylation of the relatively planar dienolate occurs from the face opposite the 4a-aryl substituent. The stereochemistry at C-7 of the minor product **13a** could not be determined in this case but is assigned by analogy with the other γ-alkylation products. Reaction of the dienolate with ethyl iodide (Table 1, entry 2) gave a mixture of **12b** and **13b** in 54% yield and a ratio of 5:3 in favour of **12b**. The stereochemistry of **12b** was again assigned by the shift of the C-6 methyl group and the availability of sufficient quantities of pure **13b** allowed extensive NOE experiments to be carried out. These showed clear NOES between the C-6 methyl and the C-7 proton, between the C-6 and C-7 protons and between the C-6 methyl

Table 1. Alkylation of the dienolate of **9**,[12] Scheme 2

Entry	R-Br	Ratio **12:13**	Combined yield (%)
1	CH_3-I	9:1	58
2	CH_3CH_2-I	5:3	54
3	CH_2=$CHCH_2$-Br	2.2:1	48
4	$PhCH_2$-Br	2.1:1	58
5	$CH_3(CH_2)_3$-I	1:1	59



Scheme 3.

and the pseudo-equatorial C-5 proton. These indicate that the C-7 ethyl group and the C-6 methyl group are in a *trans*-relationship and pseudo-diaxial. This agrees with the approach of the ethyl iodide being to the lower face of the dienolate in a pseudo-axial manner. Reaction of the dienolate with allyl bromide gave the two allylated adducts in a combined isolated yield of 48% and a ratio of 2.2:1 favouring the α-alkylation product **12c**. Similarly, reaction with benzyl bromide gave a mixture of **12d** and **13d** in 58% yield with **12d** as the major regioisomer (2.1:1). Finally, the dienolate was reacted with 1-iodobutane (Table 1, entry 5), a considerably less reactive alkyl halide. This led to a combined yield for **12e** and **13e** of 59% easily comparable to the more reactive alkyl halides, but in this case a 1:1 mixture of α- to γ-alkylation was observed. An attempt to use 2-iodopropane as the electrophile gave no sign of any alkylation product and we assume that elimination predominates with such secondary halides. The trend in regioselectivity observed in these experiments, ranging from ca. 9:1 α-:γ-selectivity for methyl iodide to equal amounts of α- and γ-alkylation with 1-iodobutane, mirrors that reported Parra et al.[11] They also report that allylic and benzylic halides give significant amounts of γ-alkylation product. The two adducts formed by allylation of the dienolate could feasibly interconvert via a Cope rearrangement in which the α-adduct reduces the strain associated with the quaternary centre at C-8a and brings the double bond into conjugation with the carbonyl group. However, no interconversion of the two regioisomers was found upon standing in solution at room temperature, indicating that these are true kinetic ratios in this system.

The success obtained in alkylation of the dienolate derived from **9** encouraged us to explore the electrophilic hydroxylation of this intermediate. A number of reagents have been used to hydroxylate enolate species including MoOPH[13] and the Davis oxaziridine **14**.[14] We chose the oxaziridine and reacted this with the dienolate at −10°C. This gave rise to 38% of the α-hydroxylated adduct **15** and 35% of the γ-hydroxylated adduct **16** (Scheme 3). As with the alkylation products, the stereochemistry in **15** was evident from the doublet at δ 0.29 assigned to the C-6 methyl group. The relative stereochemistry of **16** could not be determined with certainty and is assigned by analogy with the γ-alkylation products.

In summary, we have explored the introduction of substituents at the C-8a position of the 4a-aryloctahydroisoquinoline system using dienolate chemistry. The regioselectivity of these reactions has been explored and the hydroxylation of this ring junction position to give an analogue of **5** has been achieved.

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12. A typical procedure is as follows: LHMDS (0.2 mL, 0.2 mmol, 1 M solution in THF) was added to a cooled (0°C) solution of lactam **9** (50 mg, 0.175 mmol) in dry THF (3 mL) under nitrogen. The solution became dark orange and was stirred for 40 min at 0°C. Ethyl iodide (30 mg, 0.2 mmol) was added and the reaction warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous ammonium chloride (2 mL) and the THF removed under reduced pressure. The residue was partitioned between ether and water and the product extracted in the usual way. Evaporation of the organic solution gave an oil which was purified by column chromatography (1:1 ethyl acetate:hexane) to give α-alkylated product **12b** (15.7 mg, 30%) and γ-alkylated product **13b** (10.7 mg, 18%) as pale oils. Data for **12b**: ν_{max} (cm^{-1}) 1645 (C=O), 1600 (C=C); δ_H ($CDCl_3$) 0.29 (3H, d, *J* 7.5, C-6 methyl), 0.97 (3H, t, *J* 7.5, CH_2CH_3), 1.68–1.87 (2H, m, CH_2CH_3), 1.89 (1H, m, C(5)-H), 1.95 (1H, dd, *J* 14 and 6.5, C(4)-H), 2.30–2.37 (1H, m, C(5)-H), 2.35 (1H, dd, *J* 14 and 9, C(4)-H),

2.19–2.24 (1H, m, C(6)-H), 2.60 (1H, dt, *J* 12 and 6.5, C(3)-H), 2.66 (3H, s, NMe), 3.04–3.09 (1H, m, C(3)-H), 3.73 (3H, s, OMe), 5.36, (1H, dd, *J* 10 and 2.5, C(7)-H), 6.64 (1H, m, C(8)-H), 6.64–7.12 (4H, m, aryl-H); δ_C 9.3 (CH_3), 21.4 (CH_3), 27.8 (CH), 32.0 (CH_2), 33.1 (CH_2), 34.5 (CH_3), 38.6 (CH_2), 44.0 (C-quaternary), 46.5 (CH_2), 46.6 (C-quaternary), 55.2 (CH_3), 111.0 (CH), 115.2 (CH), 121.6 (CH), 128.2 (CH), 128.6 (CH), 130.8 (CH), 146.3 (C-quaternary), 158.7 (C-quaternary), 173.8 (CO); Found: M^+, 313.2054. $C_{20}H_{27}NO_2$ requires 313.2042. Data for **13b**: ν_{max} (cm^{-1}) 1662 (C=O), 1610–1590 (C=C); δ_H ($CDCl_3$) 0.74 (3H, d, *J* 6.5, C-6 methyl), 0.95 (3H, t, *J* 7.5, CH_2CH_3), 1.35–1.43 (2H, m, C(6)-H and CH_2CH_3), 1.52–1.69 (1H, m, CH_2CH_3), 1.64 (1H, dd, *J* 13.5 and 9, C(5)-H), 1.65–1.71 (1H, m, C(7)-H), 1.83 (1H, dd, *J* 13.5 and 4, C(5)-H), 2.15 (2H, m, C(4)-H), 2.73 (3H, s, NMe), 2.85–3.00 (2H, m, C(3)-H), 3.77 (3H, s, OMe), 6.7 (4H, m, aryl-H), 6.96 (1H, d, *J* 3, C(8)-H); δ_C 10.9 (CH_3), 20.1 (CH_3), 25.9 (CH_2), 30.6 (CH), 34.5 (CH_3), 35.9 (CH_2), 42.3 (C-quaternary), 43.8 (CH), 45.9 (CH_2), 46.2 (CH_2), 55.2 (CH_3), 111.2 (CH), 112.1 (CH), 118.5 (CH), 129.5 (CH), 134.5 (C-quaternary), 139.5 (CH), 147.8 (C-quaternary), 159.8 (C-quaternary), 166.1 (CO); found: M^+, 313.2048. $C_{20}H_{27}NO_2$ requires 313.2042.

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