Pergamon

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Tetrahedron Letters 44 (2003) 7803–7807

TETRAHEDRON LETTERS

Asymmetric synthesis of the erythrinan alkaloid system using a chiral lithium amide base desymmetrisation as the key step

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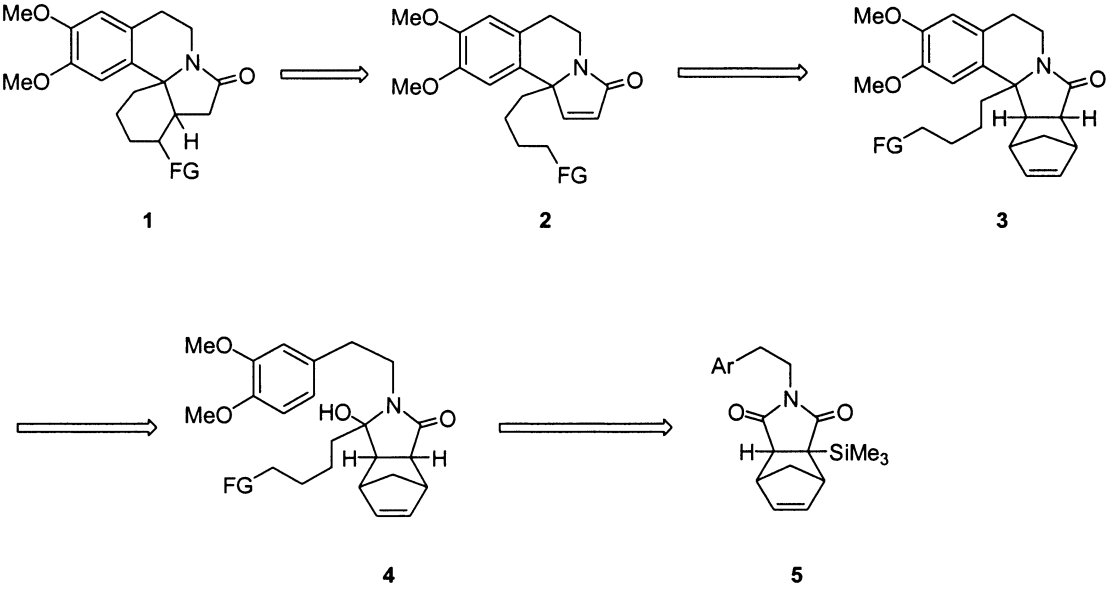
Received 30 July 2003; accepted 14 August 2003

Abstract—A new asymmetric approach to the erythrinan alkaloid system is described, which involves chiral base desymmetrisation of a ring fused imide and a *6-exo-trig* radical cyclisation as the key steps.

The pyrrolo[2,1-*a*]isoquinoline structure is a significant motif present in the *erythrina* alkaloid group,[1] as well as representing a biologically active system in its own right.[2] Lete and co-workers have proposed that unsaturated pyrrolo[2,1-*a*]isoquinolones of general structure **2** could represent useful precursors to the complete erythrinan skeleton **1** by cyclisation of the functionalised side chain onto the lactam ring in a Michael type fashion.[3–5] Although this research group has published a series of studies aimed at achieving this objective, it has not been accomplished to date, as far as we are aware.

We became interested in the asymmetric synthesis of structures **2**, since it seemed possible to access such intermediates by our recently developed chiral lithium amide base-mediated desymmetrisation of ring-fused imides.[6,7] Our approach is outlined in retrosynthetic form in Scheme 1.



Scheme 1.

Keywords: chiral lithium amide base; erythrinan alkaloid; radical cyclisation.
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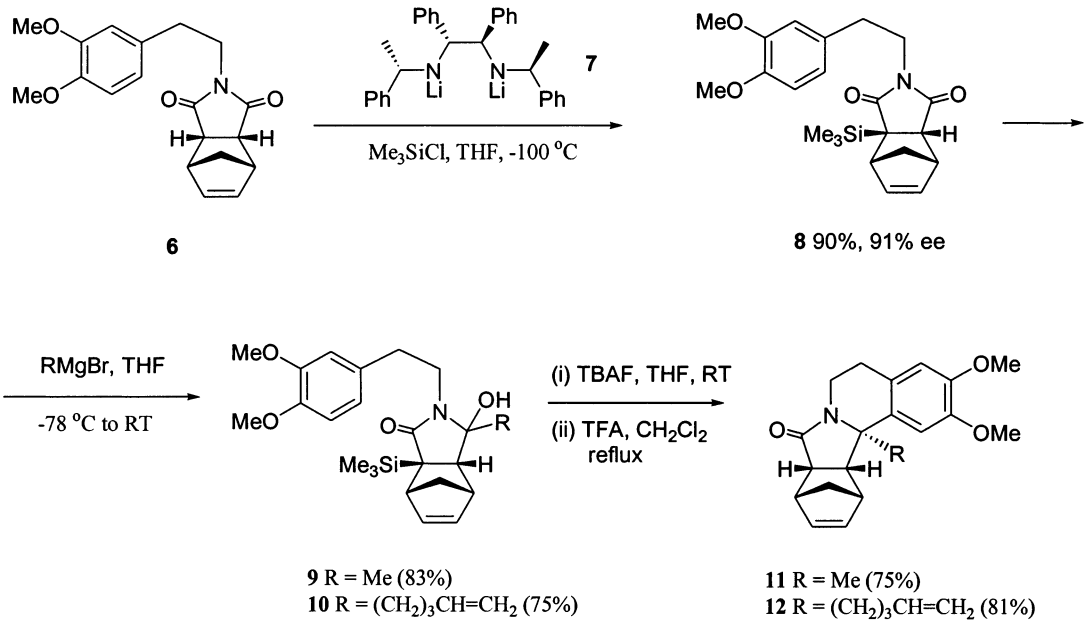
doi:10.1016/j.tetlet.2003.08.078



Scheme 2.

Access to the required intermediates **2** would be by retro-Diels–Alder reaction of the cyclopentadiene adduct **3**, which in turn would arise by cyclisation of **4** via an *N*-acyliminium ion intermediate. Compound **4** would be prepared by addition of a suitable Grignard reagent to imide **5**, which would be available in high levels of enantiopurity from the corresponding simple *meso*-imide by application of our earlier chiral base chemistry.

In the forward sense we expected that the stereochemical control would arise from initial Grignard reaction distal to the controlling trimethylsilyl group of **5**, followed by *exo*-selective cyclisation of the aromatic appendage onto the tricyclic nucleus. The final cyclisation of **2** to give **1** appeared constrained to give only a single cyclohexane product with respect to the new ring fusion. Since Lete and co-workers had demonstrated the viability of this type of *N*-acyliminium ion cyclisation and retro Diels–Alder process,[3–5] the key issues to be addressed were the nature of the functionality FG and choice of reaction mode for the final cyclisation.

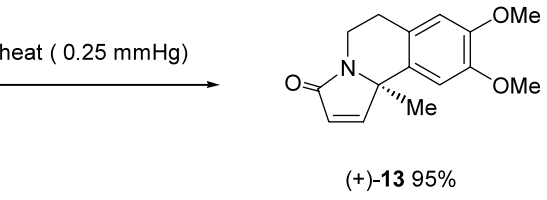
This approach would enable a very rapid asymmetric access to the key pyrrolo[2,1-*a*]isoquinolones, and might allow us to incorporate a choice of side chains appropriate for completion of the erythrinan skeleton. Also, the chiral base approach would allow the preparation of either enantiomeric series. Here we describe the successful implementation of this plan, which has resulted in a short, completely stereocontrolled route to a functionalised tetracyclic intermediate with great potential for synthesis of naturally occurring alkaloids.

Chiral base reaction of imide **6** using the bis-lithium amide **7** gave the desired silylated product (–)-**8** in 90% yield and 91% ee, Scheme 2.[8]

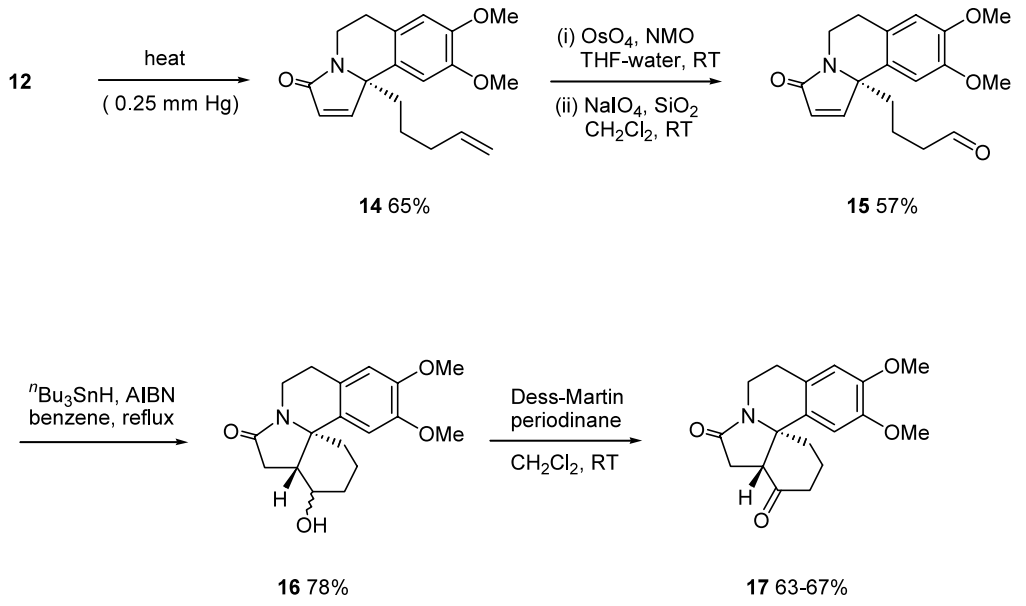
At this stage the absolute configuration of **8** was assigned by analogy to our previous work on the corresponding *N*-phenyl imide,[6] but this was later confirmed by correlation with known compounds (see below). Reaction of excess Grignard reagent with imide **8** occurred with very high regioselectivity (none of the minor regioisomer could be observed by ^{1}H NMR) to give hydroxylactam intermediates **9** or **10**. Cyclisation of these intermediates was best accomplished after desilylation, to give the pentacyclic products **11** and **12** in good yields and with complete diastereocontrol. In the case of **10** it was especially significant that clean cyclisation of the aromatic group occurred onto the *N*-acyliminium intermediate, without interference from the alkenyl side-chain that would lead to spiro-fused products. This was a key aspect of our choice of a relatively unreactive side chain, since Lete and co-workers had previously demonstrated that compounds with an alkenylsilane side chain show the unwanted (in this context) spiro mode of cyclisation.

The identity of intermediate **11** was then confirmed by Diels–Alder cycloreversion by heating under reduced pressure (Scheme 3).

This gave the known unsaturated lactam **13**, which had spectroscopic data in accord with those published by Lete and co-workers. We were also able to confirm our



Scheme 3.



Scheme 4.

assignment of absolute stereochemistry by comparison of $[\alpha]_D$ data.[9]

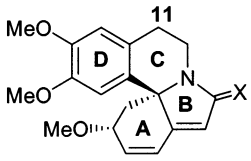
With the key stereochemical features of the synthesis established we then transformed the lactam with the appended unsaturated side chain as shown in Scheme 4.

Retro-Diels–Alder of **12** reaction proceeded to give **14**, the side chain of which was then cleaved by a conventional two-step oxidation, to give aldehyde **15**. Lete and co-workers had previously conceived a ring closure of this type of system via a dithiane anion, but we chose instead to conduct a reductive cyclisation under free radical conditions.

Thus, exposure of aldehyde **15** to tributyltin hydride, under conditions described by Muller et al. for cyclisation of 5′-aldehyde nucleosides led efficiently to the desired hydroxy lactam **16** as a mixture of diastereomers at the newly formed carbinol centre.[10–12] This outcome was especially welcome, since successful *6-exo-trig* closures are rare compared to the *5-exo-trig* variants, and is probably due in part to the lack of a competing 1-5 hydrogen atom abstraction process in our system.

In order to transform the mixture of alcohols **16** (ca. 3:1 mixture) into a single substance we also carried out the oxidation of the separated compounds, each of which gave the same ketone product **17**.[13,14]

The formation of **16** represents the completion of the full erythrinan skeleton in a highly stereocontrolled fashion and a relatively short overall sequence (eight steps from simple imide **6**). Naturally occurring alkaloids (which are of the opposite enantiomeric series to the ones made here), often incorporate unsaturation in the A and B rings, e.g. erysotrine **18** and erysotamidine **19**, and may also possess C-11 oxygenation.[1]



18 X = CH_2
19 X = C=O

Considering the well-established repertoire of transformations established for intermediates related to these compounds, we believe that the functional group 'handles' installed in our intermediates should be attractive for the synthesis of natural products and their relatives.[15] Thus, we anticipate that the strategy described above should be a fruitful source of enantiomerically pure alkaloids of this family. Extension of this desymmetrisation strategy to include other types of alkaloid is planned.

Acknowledgements

We thank the Engineering and Physical Sciences Research Council (EPSRC) for support of C.D.G., and we thank the University of Nottingham for support of D.A.G.

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8. In previous work (Ref. 6) we used a simpler chiral base (bis-phenethylamine) to access *N*-phenyl and *N*-benzyl derivatives related to **8** in very high yields and ee. With the modified nitrogen substituent required for the present synthesis we were unable to obtain high chemical yields using that procedure, and found that the dilithiated chiral base **7** gave the best compromise in terms of workable synthetic yield without too great a loss of ee.
*Typical procedure for the silylation of **6** to give **8**.*
Chiral lithium amide base **7** was prepared from the corresponding chiral amine (622 mg, 1.48 mmol) in THF (6 mL) and *n*-BuLi (1.9 mL of a 1.5 M solution in hexanes, 2.89 mmol). The resulting solution of the chiral base **7** was then cooled to −100°C, before being added dropwise via cannula over 15 min to a stirred solution of the imide **6** (402 mg, 1.23 mmol) and freshly distilled trimethylsilyl chloride (1.57 mL, 12.3 mmol) in THF (12 mL), maintaining a temperature of −100°C±1. The reaction mixture was then allowed to warm to room temperature overnight, before quenching with saturated aqueous $NaHCO_3$ (10 mL) and extraction with EtOAc (3×50 mL). The extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (gradient 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether) to yield the imide **8** as a pale yellow oil (443 mg, 90%): $[\alpha]_D^{20}$ −46 (*c* 1.71 in $CHCl_3$); HRMS (EI): found M^+, 399.1854. $C_{22}H_{29}NO_4Si$ requires *M*, 399.1866. The ee was determined as 91% by HPLC (Chiracel OD column, 1% IPA in hexane, 0.8 mL/minute), the retention times were 38.2 min (minor) and 40.5 minutes (major).
9. *Preparation of (+)-**13***
Isoquinoline derivative **11** (53 mg, 0.16 mmol) was heated in a round bottomed flask by a Bunsen burner under a high vacuum (0.25 mmHg) for approximately 30 s. The progress of the reaction was monitored by ^1H NMR and the procedure repeated until evolution of cyclopentadiene ceased to be observed. The dark coloured crude dihydropyrrolo[2,1-*a*]isoquinolinone was dissolved in dichloromethane (10 mL), decolourising charcoal was added and the resultant reaction mixture heated to reflux with stirring. After 10 min the mixture was filtered hot, concentrated in vacuo and the procedure repeated twice more until the crude product had become a dark yellow colour. The crude product was then purified via flash column chromatography using silica gel (80% EtOAc/petroleum ether) to yield dihydropyrrolo[2,1-*a*]-isoquinolinone **13** as a pale yellow oil (40 mg, 95%): $[\alpha]_D^{20}$ +222 (*c* 0.39 in $CHCl_3$), lit.[3] $[\alpha]_D^{20}$ +202.8 (*c* 1.43 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2935 and 2852 (C-H), 1680 (C=O), 1613 and 1503 (Ar); δ_H (500 MHz) 1.61 (3H, s, CH_3), 2.68 (1H, dd, *J* 16.0, 4.3, $CH_2CH_AH_BAr$), 2.94 (1H, ddd, *J* 16.0, 12.0, 6.5, $CH_2CH_AH_BAr$), 3.24 (1H, ddd, *J* 13.2, 12.0, 4.3, $CH_AH_BCH_2Ar$), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.44 (1H, dd, *J* 13.2, 6.5, $CH_AH_BCH_2Ar$), 6.12 (1H, d, *J* 5.8, HC=CH), 6.61 (1H, s, ArC*H*), 6.65 (1H, s, ArC*H*), 7.36 (1H, d, *J* 5.8, HC=C*H*); δ_C (125.8 MHz) 26.8 (*C*H$_3$), 29.3 (CH_2CH_2Ar), 34.7 (CH_2CH_2Ar), 55.9 (O*C*H$_3$), 56.2 (O*C*H$_3$), 65.6 (*C*NMe), 108.7 (Ar*C*H), 111.9 (Ar*C*H), 125.1 (Ar*C*), 125.2 (H*C*=CH), 129.1 (Ar*C*), 147.6 (Ar*C*), 148.0 (Ar*C*), 153.3 (HC=*C*H), 170.3 (*C*=O); MS (EI) *m*/*z* 259 (M^+, 49%), 245 (45), 244 (M−CH_3, 100), 228 (M−OCH_3, 12), 200 (20), 122 (14), 57 (14) (HRMS: found M^+, 259.1203. $C_{15}H_{17}NO_3$ requires *M*, 259.1209).
The ee of this product was determined to be 85% by HPLC (Chiracel OD column, 20% IPA in hexane, 0.4 mL/minute), the retention times were 25.8 min (minor) and 31.7 min (major). We need to check further if the apparent slight loss of stereochemical integrity (91% ee to 85% ee) is real.
10. Muller, E.; Gasparutto, D.; Jaquinod, M.; Romieu, A.; Cadet, J. *Tetrahedron* **2000**, *56*, 8689.
11. *Radical cyclisation of aldehyde **15**.*
To a stirred solution of aldehyde **15** (145 mg, 0.46 mmol) in dry, degassed, benzene (20 mL) under Ar, at reflux, was added a solution of ^{n}BuSnH (0.25 mL, 0.93 mmol) and AIBN (76 mg, 0.46 mmol) in dry, degassed benzene (20 mL) over 6 h via a syringe pump. The reaction mixture was heated at reflux for a further 16 h then allowed to cool to room temperature and concentrated in vacuo. Purification by flash silica column chromatography (CH_2Cl_2 then 1 to 4% MeOH gradient) gave a partially separable mixture of epimeric alcohols **16** in the ratio 3:1, in addition to traces of non-cyclised alcohol (∼5%), in a combined yield of 114 mg (78%).
Data for major diastereoisomer; oil; $[\alpha]_D^{29}$ +88.5 (*c* 0.8 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3617 (OH), 2937 (CH), 1681 (C=O), 1464, 1359, 1122, 1052, 1004, 894; δ_H (500 MHz) 1.42–1.46 (1H, m), 1.56–1.63 (1H, m), 1.71 (1H, ddd, *J* 18.1, 9.0, 4.4), 1.77 (1H, ddd, *J* 14.7, 11.3, 3.7), 2.00 (2H, app. dt, *J* 13.5, 4.3), 2.35–2.37 (2H, m), 2.49 (1H, ddd, *J* 6.8, 6.8, 4.6), 2.57 (2H, dd, *J* 17.1, 4.1), 3.06 (1H, ddd, *J* 16.4, 11.2, 7.3), 3.18 (1H, ddd, *J* 13.3, 11.2, 5.5), 3.72-3.76 (1H, m), 3.83 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 4.18 (1H, ddd, *J* 13.3, 7.3, 1.5), 6.52 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*); δ_C (125 MHz) 18.2 (CH_2), 26.3 (CH_2), 31.8 (CH_2), 35.0 (CH_2), 35.6 (CH_2), 35.8 (CH_2), 44.9 (CH), 55.9 (CH_3), 56.2 (CH_3), 64.9 (C), 71.1 (CH), 109.8 (CH), 111.8 (CH), 125.8 (C), 133.6 (C), 147.5 (C), 147.9 (C), 176.2 (C=O); EIMS (*m*/*z*) 317 (M^+, 56%), 274 (100%), 244 (79%); (HRMS M^+ 317.1621, $C_{18}H_{23}NO_4$ requires 317.1627).
Data for minor diastereoisomer; oil; $[\alpha]_D^{30}$ +66.0 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3507 (OH), 2938 (CH), 1672 (C=O), 1463, 1361, 1049, 908; δ_H (500 MHz) 1.47–1.70 (4H, m), 1.92–1.98 (1H, m), 2.01–2.05 (1H, m), 2.40 (1H, br.s, disappears on D_2O shake, OH), 2.45 (1H, dd, *J* 17.1, 9.5), 2.63 (1H, dd, *J* 17.1, 10.2), 2.74 (1H, app. dt, *J* 16.2, 4.6), 2.82 (1H, ddd, *J* 9.6, 9.6, 5.6), 2.92 (1H, ddd, *J* 16.2,

9.7, 6.6), 3.21 (1H, ddd, *J* 13.0, 9.7, 5.6), 3.86 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 4.06 (1H, ddd, *J* 13.0, 6.7, 4.0), 4.52 (1H, m), 6.61 (1H, s, Ar*H*), 6.78 (1H, s, Ar*H*); δ_C (125 MHz) 18.8 (CH_2), 27.8 (CH_2), 28.2 (CH_2), 31.5 (CH_2), 35.1 (2×CH_2), 45.0 (CH), 55.9 (CH_3), 56.4 (CH_3), 64.2 (C), 68.7 (CH), 108.6 (CH), 112.0 (CH), 125.6 (C), 134.4 (C), 147.6 (C), 148.0 (C), 172.3 (C=O); EIMS (*m*/*z*) 317 (M^+, 28%), 274 (100%), 245 (35%); (HRMS M^+ 317.1618, $C_{18}H_{23}NO_4$ requires 317.1627).

12. This mixture of epimeric alcohols has been reported previously in racemic form, see: Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, H. J.; Vilhuber, H. G.; Bottcher, K. *Chem. Ber*. **1970**, *103*, 615.
13. *Oxidation of the minor diastereomer of* ***16*** *to give ketone* ***17***

    To a stirred suspension of Dess–Martin periodinane (31 mg, 0.07 mmol) in CH_2Cl_2 at room temperature under N_2 was added a solution of alcohol **16** (19 mg, 0.06 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 30 min then quenched with saturated aqueous sodium thiosulfate solution (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash silica column chromatography (0.5 then 1% MeOH in CH_2Cl_2) gave ketone **17** as a colourless oil (10 mg, 63%); $[\alpha]_D^{23}$ +52.2 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2938 (CH), 1720, 1682 (C=O), 1464, 1361, 1122, 907, 869; δ_H (500 MHz) 1.86–1.97 (3H, m), 2.18–2.23 (1H, m), 2.49–2.55 (1H, m), 2.63 (1H, dd, *J* 17.5, 10.4), 2.69-2.77 (2H, m), 2.78 (1H, dd, *J* 17.5, 7.8), 2.97 (1H, ddd, *J* 16.7, 10.9, 7.0), 3.16 (1H, app. t, *J* 9.4), 3.26 (1H, ddd, *J* 13.1, 10.9, 5.1), 3.83 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 4.21 (1H, ddd, *J* 13.1, 7.0, 2.6), 6.45 (1H, s, Ar*H*), 6.58 (1H, s, Ar*H*); δ_C (125 MHz) 18.7 (CH_2), 27.1 (CH_2), 34.3 (CH_2), 35.3 (CH_2), 36.1 (CH_2), 37.8 (CH_2), 53.3 (CH), 56.0 (CH_3), 56.1 (CH_3), 66.2 (CH), 108.0 (CH), 111.7 (CH), 125.2 (C), 133.1 (C), 148.1 (C), 148.4 (C), 171.6 (C=O), 210.6 (C=O); EIMS (*m*/*z*) 315 (M^+, 39%), 272 (39%), 245 (100%), 151 (19%); (HRMS M^+ 315.1470, $C_{18}H_{23}NO_4$ requires 315.1471).
14. This ketone has been reported previously in racemic form, see: (a) Mondon, A.; Bottcher, K. *Chem. Ber*. **1970**, *103*, 1512; (b) Kametani, T.; Higashiyama, K.; Honda, T.; Otomasu, H. *Heterocycles* **1984**, *22*, 569.
15. See for example: Isobe, K.; Mohri, K.; Takeda, N.; Suzuki, K.; Hosoi, S.; Tsuda, Y. *Chem. and Pharm. Bull*. **1994**, *42*, 197.