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NOVEL APPROACH TO TRANS-FUSED CARBOBICYCLES

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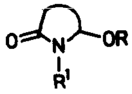
Abstract: The combination of a silicon directed N-acyliminium ion cyclization reaction and a subsequent S_N2' substitution of an imide nitrogen with lithium dimethyl cuprate constitutes a novel approach to functionalized trans-fused carbobicycles.

Recently[1], we reported on the promising synthetic utility of ω-alkoxy lactams of type 1, which can serve as dipolar conjunctive reagents. We here describe in the first place the successful application of this novel annulation methodology to bicyclic ethoxy lactams 2, which leads to allenic nitrogen compounds 7 and 8. The principal feature of this paper is the disclosure of an unprecedented allylic substitution reaction of these latter compounds with lithium dimethyl cuprate.

Deprotonation of ethoxy lactams 2[2] using LDA in THF was virtually complete



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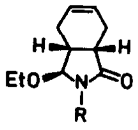
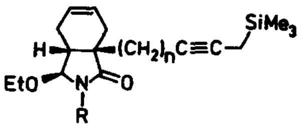
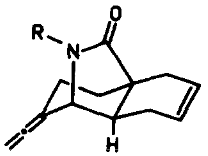
$I(CH_2)_nC\equiv CCH_2SiMe_3$

3 n=2
4 n=3





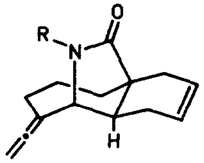


2a R=CH_2Ph
2b R=$SiMe_3$

5a R=CH_2Ph ; n=2
5b R=H ; n=2
6 R=H ; n=3

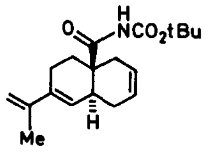
7a R=CH_2Ph
7b R=H
7c R=CO_2tBu

in 30 min at -78°C. Alkylation with iodide 3 (1h, -78°C; 1 h, -78°C → 0°C) afforded 5a in 55% yield[5] as a single isomer. Literature precedent on the angular alkylation of isobenzofuranones[6] and isoindolones[7], as well as NMR evidence[8] led us to assume a cis ring junction stereochemistry for 5a. Upon stirring in formic acid for 30 min 5a was converted into tricyclic allenic amide 7a[5] in 97% yield[1,9]. Since attempted reductive removal (Na, NH_3)[10] of the N-benzyl group was found to result instead in cleavage of the α-allenic carbon nitrogen bond[11], we repeated the above reaction sequence starting with trimethylsilyl protected 5b. Alkylation of its enolate with 3 and 4, followed by N-desilylation (2% aqueous NaOH) led to 5b[5] (79%) and 6[5] (57%) as single isomers for which we again assume the cis ring junction (vide supra). Ring closure was readily achieved in formic acid to give 7b[5] (91%) and 8a[5] (100%).



8a R=H

8b R=CO_2tBu



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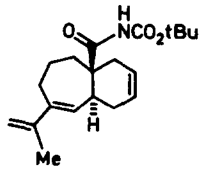

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Since lactams 7 and 8 in essence are derivatives of trans-fused carbobicycles, a general entry into the latter category of materials is at hand, provided the lactam ring can be transformed in a useful manner. This objective was realised in the following way. The lactam nitrogen was protected and its leaving group ability enhanced by introduction of the t-butoxycarbonyl group[12], furnishing 7c[5] (89%) and 8b[5] (94%). When 7c was added at -78°C to a solution of 1.5 eq of lithium dimethyl cuprate in ether, a fast reaction ensued (90 min, -78°C; 30 min, -78°C → -40°C) to afford in 75% yield bicyclic 9[5] as a white crystalline solid. Similarly, 8b gave 10[5] in 91% yield.

There are several interesting points associated with this novel cuprate reaction[13]. To the best of our knowledge this is the first example in which an amide (imide) nitrogen serves as a leaving group in a cuprate allylic substitution reaction[14]. Complete γ-regioselectivity is observed, which has been found also in similar reactions of derivatives of α-allenic alcohols[15]. The products are 1,3-dienes and thus well suited for further (Diels Alder) chemistry. Finally, our methodology offers a fully stereoselective access to angular functionalized trans-fused carbobicycles in a small number of steps starting from readily obtainable ω-ethoxy lactams.

Scope and applications are currently investigated.

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2. Commercially available cis-1,2,3,6-tetrahydrophthalimide was the starting material for **2a** and **2b**. Benzylation ($PhCH_2Cl$, K_2CO_3, acetone) followed by $NaBH_4$ reduction[3] and ethanolysis afforded **2a**. Reduction ($NaBH_4,H^+$)[3], ethanolysis and trimethylsilylation ($((Me_3Si)_2NH)$[4], respectively, gave **2b**.

3a) J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, *Tetrahedron*, **31**, 1437 1975.

b) J.B.P.A. Wijnberg, H.E. Schoemaker and W.N. Speckamp, *Ibid*., **34**, 179 (1978).

4. T. Nagasaki, S. Esumi, N. Ozawa, Y. Kosugi and F. Hamaguchi, *Heterocycles*, **16**, 1987 (1981).

5. Yields are given for purified (flash chromatography) products (except for **8a**, which as crude material was virtually pure), which showed satisfactory spectral and exact mass data. Some selected data are: **5a** (oil): IR($CHCl_3$) 2210, 1685, 1245, 850 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.30 (m, 5H), 5.62--6.04 (m, 2H), 4.99 (d, J=15 Hz, 1H), 4.16 (d, J=3 Hz, 1H), 3.99 (d, J=15 Hz, 1H), 3.46 (m, 2H), 1.68-2.53 (m, 9H), 1.42 (t, J=2.5 Hz, 2H), 1.20 (t, J=7 Hz, 3H), 0.10 (s, 9H). **6** (oil): IR($CHCl_3$) 3450, 2210,1700, 1250, 850 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.30 (br s, 1H), 5.90 (m, 2H), 4.48 (d, J=3 Hz, 1H), 3.3-3.7 (m, 2H), 1.5-2.5 (m, 11H), 1.40 (t, J=2.5 Hz, 2H), 1.23 (t, J=7 Hz, 3H) 0.08 (s, 9H). **7b** (mp 150-2°C): IR($CHCl_3$) 3430, 3220, 1970, 1710 cm^{-1}; ^1H NMR($CDCl_3$) δ 6.96 (br s, 1H), 5.50-5.82 (m, 2H), 4.60-4.86 (m, 2H), 3.78 (br s, 1H), 1.60-2.80 (m, 9H); ^{13}C NMR($CDCl_3$) δ 201.9 (s), 179.4 (s), 125.1 (d), 124.9 (d), 99.2 (s), 76.0 (t), 59.5 (d), 46.0 (d), 44.1 (s), 34.1 (t), 28.2 (t), 25.7 (t), 24.4 (t). **8a** (oil): IR($CHCl_3$) 3450, 3210, 1975, 1710 cm^{-1}; ^1H NMR($CDCl_3$) δ 6.1 (br s, 1H), 5.75 (m, 2H), 4.70 (m, 2H), 3.86 (br s, 1H), 1.20-2.80 (m, 11H). **9** (mp 134-7°C): IR($CHCl_3$) 3350, 1780, 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (br s, 1H), 5.84 (m, 1H), 5.72 (m, 2H), 5.05 (m, 1H), 4.97 (m, 1H), 1.95 (s, 3H), 1.45 (s, 9H), 1.14-3.02 (m, 9H). **10** (oil): IR($CHCl_3$) 3340, 1785, 1710 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.0 (br s, 1H), 5.60 (m, 3H), 5.02 (br s, 1H), 4.92 (br s, 1H), 1.90 (s, 3H), 1.45 (s, 9H), 1.1-3.2 (m, 11H).

^{13}C NMR($CDCl_3$) δ 173.1 (s), 149.3 (s), 144.6 (s), 143.8 (s), 128.6 (d), 126.2 (d), 125.8 (d), 112.3 (t), 81.9 (s), 50.4 (s), 38.9 (t), 36.9 (d), 35.5 (t), 31.4 (2 x t), 28.0 (3 x q), 21.3 (q), 20.4 (t).

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8. The magnitude of the vicinal coupling constant[5] of the CHOEt hydrogen with the adjacent angular hydrogen is indicative of the stereochemistry of ring junction: R. Brettle and S.M. Shibib, *J.Chem.Soc.Perkin I*, 2912 (1981).

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   - c) A.D. Despo, S.K. Chiu, T. Flood and P.E. Peterson, *Ibid*, **102**, 5120 (1980).

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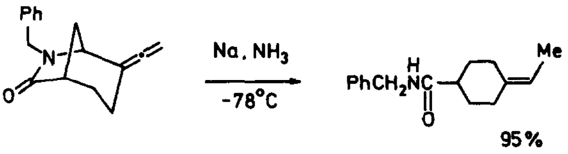
11. Details of this interesting transformation (an example is shown below) will be given in our full paper.



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