Pergamon

Tetrahedron Letters, Vol. 38, No. 32, pp. 5709-5712, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01252-5

Regiocontrol in the Rhodium (II) Catalysed Reactions of 1,2,3,4-Tetrahydro-1-Naphthyl Diazomethyl Ketones: Potential Applications to the Synthesis of *Galbulimima* Alkaloids

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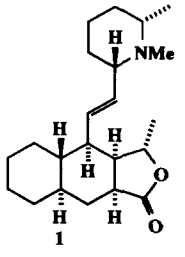
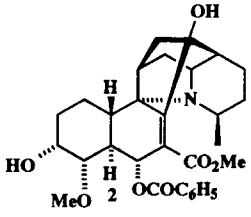
Abstract: The selectivity of diazoketone derived rhodium-carbenoid insertions into aromatic and aliphatic C-H bonds has been shown to be sensitive to the total steric environment of the participating groups and may be controlled by varying the steric bulk of the ligands on rhodium. © 1997 Elsevier Science Ltd.

Structures **1** - **4** are representative of a family of alkaloids isolated from the bark of the Northern Queensland and Papua New Guinea rain forest tree, *Galbulimima belgraveana*.[1] Considerable interest is presently centred on himbacine (**1**), a potent muscarinic antagonist and a lead compound in the search for drugs to treat Alzheimer's disease,[2] and as a consequence, two total syntheses have been completed recently.[3,4] Our own interests have been concerned with the synthesis of the more complex alkaloids **2**,[5] **3**[6] and **4**[7] and in this Letter we describe some preliminary experiments directed towards the assembly of **4**.[8]



1



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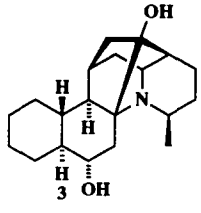

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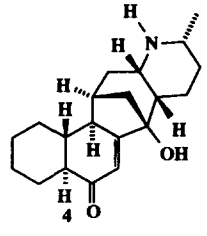
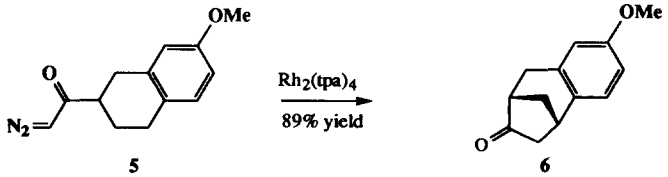


4

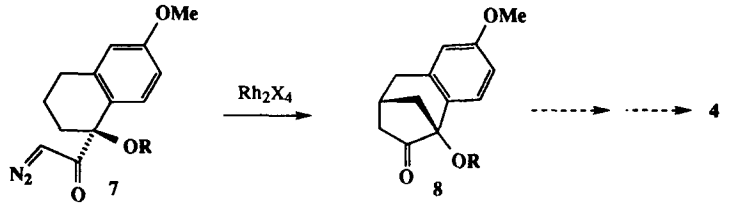
Having shown that the bicyclic ketone **6** could be prepared in excellent yield by the rhodium(II) catalyzed CH insertion reaction of diazoketone **5** (Scheme 1),[9] we have embarked upon the investigation of the analogous process for diazoketone **7** in the hope of establishing an equally expeditious synthesis of ketone **8** and thence **4** (Scheme 2). Elaboration of the decalin ring system onto such a product should be straightforward, while the anisole moiety should serve either as a precursor to the piperidine ring or as a model for an alternative synthon. However, unlike the conversion of **5** into **6**, for which the main competitive process is cyclopropanation, it was apparent that a major issue in the proposed synthesis would be selectivity between aliphatic and aromatic C-H insertion.[10]

Scheme 1

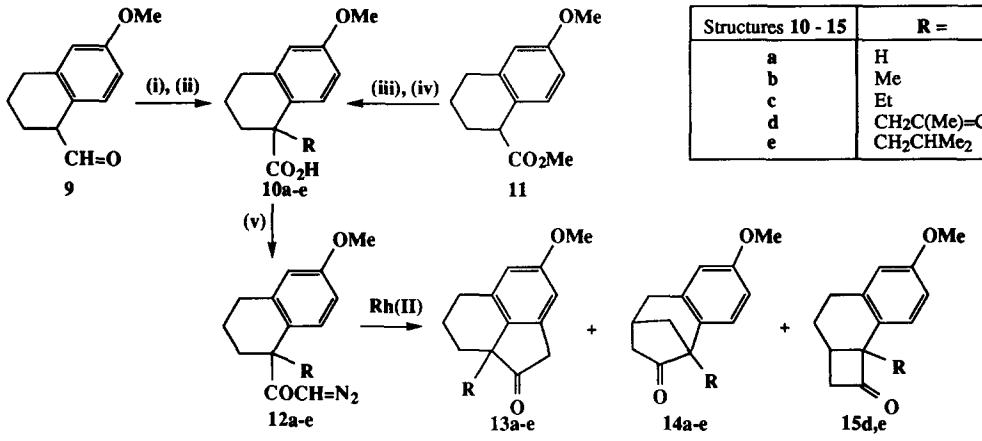


5 **6**

Scheme 2



When our attempts to assemble diazoketone **7** were frustrated by the marked tendency of precursors to undergo dehydration, we elected to examine the behaviour of the 1-alkyl analogues **12a-e** in order to test the feasibility of the basic premise. The preparation of these compounds and their reactions with various rhodium catalysts are outlined in Scheme 3. C-Alkylation of either the readily available aldehyde **9**[11] or the corresponding methyl ester **11**,[12] followed by Jones' oxidation in the first case, or by hydrolysis[13] in the latter, allowed the efficient preparation of the precursor acids **10b-e**.[14]

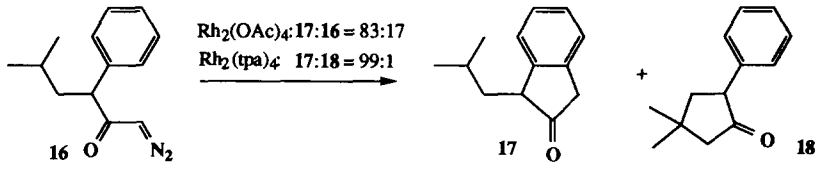


Structures 10 - 15	R =
a	H
b	Me
c	Et
d	$CH_2C(Me)=CH_2$
e	CH_2CHMe_2

Scheme 3. *Reagents*: (i) 1.5 equiv. LiO-*t*-Bu, DME; R-Halide, 0° → RT, 16h; (ii) Jones' reagent 1.6 equiv., acetone 0° → RT, 1h; (iii) 1.2 equiv. LiHMDS, THF, -78° 1h; R-Halide, -78° → RT 5h; (iv) excess KO-*t*-Bu, 3 equiv. H_2O, Et_2O, 0° → RT, 3d; (v) $(COCl)_2$, cat. DMF, CH_2Cl_2; excess CH_2N_2.

Initial experiments were conducted with the 1-methyl analogue, diazoketone **12b**, treatment of which with $Rh_2(OAc)_4$, afforded a 3:2 mixture of the desired ketone **14b** with **13b** (total yield: 85%). Much attention has been focussed upon controlling the regiochemistry[15,16] of the reactions of rhodium metallocarbenoids generated from diazoketones by modifying the ligands on the rhodium catalyst.[10,17,18] The 'insertion' of a rhodium carbenoid into an aromatic C-H bond may be considered to be an aromatic electrophilic substitution,[19] with $(L)_nRh^{(-)}$-$C^{(+)}$(R)COR' being regarded as the attacking species. Strongly electron withdrawing ligands would be expected to enhance the electrophilic nature of the carbenoid, thus favouring aromatic C-H 'insertion' and this was, indeed, the case with rhodium perfluorobutyrate (**13b**:**14b** = 4.5:1; 90% yield).[10] Conversely, amide type ligands were expected to boost the level of aliphatic CH insertion, but the acetamido analogue, $Rh_2(acam)_4$[20] also furnished mainly **13b** (**13b**:**14b** = 4:1; 85% yield). Ikegami and coworkers have recently carried out an extensive range of intramolecular competition reactions and found that with diazoketone **16**, for example, the ratio of aromatic C-H insertion product **17** to aliphatic C-H insertion product **18** could be improved from 83:17 with $Rh_2(OAc)_4$ to >100:1 by using catalysts with bulky attached ligands, *e.g.* $Rh_2(tpa)_4$ (Scheme 4).[21] In sharp contrast to this precedent, however, the use of $Rh_2(tpa)_4$ with substrate **12b**, afforded a significant increase in the yield of aliphatic CH insertion product (**14b**:**13b** = 3:1). These departures from the

Scheme 4



expected patterns of reactivity may be partly due to differences in the nature of the aliphatic C-H insertion site, but a greater factor in the behaviour of **12b** was more likely to be the steric crowding of the *peri* aromatic reaction site by the C(1) quaternary center. In order to gain further insight into these processes, therefore, the reactions of analogues of **12b**, in which the steric bulk of the C(1) alkyl group was systematically increased, were compared using $Rh_2(OAc)_4$ and $Rh_2(tpa)_4$ as catalysts. The outcomes are summarised in Table 1.

Table 1. Competitive C-H Insertion Reactions of **12a-e** Catalysed by $Rh_2(OAc)_4$ and $Rh_2(tpa)_4$

Substrate	R	Regioselectivity : $Rh_2(OAc)_4$		Regioselectivity : $Rh_2(tpa)_4$	
		13 : 14	Combined Yield (%)	**13 : 14 : 15**	Combined Yield (%)
12a	H	>10 : 1	75	2 : 1 : 0	90
12b	Me	1 : 1.5	80	1 : 3 : 0	85
12c	Et	1 : 1.5	73	1 : 8 : 0	87
12d	$CH_2CH(=CH_2)Me$	1 : 1.5	50	0 : 3 : 1	61
12e	CH_2CHMe_2	1 : 1.5	74	0 : 2 : 1	88

For **12a**, the lower steric demand of the system allowed predominantly aromatic C-H insertion (>10:1) with $Rh_2(OAc)_4$. With the bulkier $Rh_2(tpa)_4$, however, the selectivity was considerably reduced. With the remaining substrates, the $Rh_2(OAc)_4$ catalysed reactions were unaffected by the steric environment of the diazoketone, a 3:2 mixture of aliphatic to aromatic C-H insertion being obtained with **12b** - **12e** in every case. With the more sterically demanding $Rh_2(tpa)_4$ catalyst, however, the regiochemistry of the insertion was quite sensitive to relatively small changes in the substrate, and as the size of the R group increased, the proportion of aromatic C-H insertion became negligible; unexpectedly, cyclobutanones were formed in significant quantities from **12d** and **12e**. To our further surprise, there was no evidence of cyclopropanation of the pendant alkene group in substrate **12d**, nor of insertion into the tertiary C-H of the R group in **12e** with either catalyst, even though both reactions should be highly favoured.[18]

It is clear that both the nature of the substrate and the ligands on the catalyst play a critical role in determining the regiochemistry of these intramolecular rhodium carbenoid insertions. With the current choice of catalysts, however, there are good prospects that the regiochemistry can be optimized for a given objective, even though it may be necessary to take a somewhat empirical approach to the choice of catalyst. For the original purpose of synthesizing **4**, we envisage that oxidative cleavage of the side-chain in **14d** or a suitable analogue will give access to ketol **8** (R = OH). Alternatively, the cleavage could be postponed until a later stage of the synthesis.

Acknowledgement. The authors are indebted to Professor Michael Doyle for a generous gift of $Rh_2(acam)_4$.

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8. Alkaloid **4** may be cyclised under acidic conditions to form the unstable 6-one derivative of **3**.[7] It is envisaged, therefore, that as well as being a target in its own right, **4** will serve as an intermediate in the preparation of **3** and as a model system for developing approaches to **2** and its congeners.[1]
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14. Products were fully characterised by microanalysis and/or HRMS, and NMR spectra. Selected NMR data ($CDCl_3$, 300MHz; assignments of structure determined by DQCOSY, GHMQC and GHMBC at 500MHz): **10e**: ^{1}H NMR δ 1.82 (3H, d, *J* = 6.4 Hz), 1.94 (3H, d, *J* = 6.5 Hz), 1.65-2.05 (5H, m), 2.10-2.20 (1H, m), 2.25-2.35 (1H, m), 2.70-2.85 (2H, m), 3.80 (3H, s), 6.60 (1H, d, *J* = 2.8 Hz), 6.74 (1H, dd, *J* = 2.8, 8.8 Hz), 7.45 (1H, d, *J* = 8.8 Hz); ^{13}C NMR δ 19.99, 23.57, 24.65, 24.95, 30.44, 30.76, 48.39, 48.67, 55.04, 60.45, 112.07, 113.48, 129.85, 138.75, 157.86, 183.36. **12e**: ^{1}H NMR δ 0.72 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.1 Hz), 1.50-1.70 (1H, m), 1.70-2.00 (5H, m), 2.10-2.20 (1H, m), 2.75-2.85 (2H, m), 3.80 (3H, s), 4.88 (1H, s), 6.64 (d, 1H, *J* = 2.8 Hz), 6.74 (dd, 1H, *J* = 2.8, 8.7 Hz), 7.13 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR δ 20.06, 24.56, 24.69, 25.11, 30.43, 32.28, 45.92, 53.92, 54.56, 55.01, 112.01, 113.73, 129.78, 129.96, 139.57, 158.07, 200.91. **13e**: ^{1}H NMR δ 0.74 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 1.35 - 1.55 (2H, m), 1.60 - 1.85 (3H, m), 1.95 - 2.05 (1H, m), 2.05 - 2.15 (1H, m), 2.55 - 2.70 (1H, m), 2.75 - 2.90 (1H, m), 3.20 (1H, d, *J* = 21 Hz), 3.75 (1H, d, *J* = 21 Hz), 3.80 (3H, s), 6.60 (1H, s), 6.70 (1H, s); ^{13}C NMR δ 18.48, 23.50, 24.75, 24.83, 25.51, 26.37, 42.81, 46.05, 51.86, 55.33, 107.70, 111.75, 134.88, 136.20, 136.30, 159.21, 217.83. **14e** ^{1}H NMR δ 0.90 (3H, d, *J* = 6.4 Hz), 1.00 (3H, d, *J* = 6.5 Hz), 1.65 - 1.85 (2H, m), 2.00 (1H, dd, *J* = 2.4, 11.6 Hz), 2.10 - 2.15 (2H, m), 2.20 (1H, dd, *J* = 2.9, 18.6 Hz), 2.50 (1H, ddd, 1.3, 7.3, 19 Hz), 2.70 (1H, d, *J* = 17.2 Hz), 2.80 (1H, m), 3.30 (1H, dd, *J* = 4.4, 17.4 Hz), 3.76 (3H, s), 6.63 (1H, d, *J* = 2.8 Hz), 6.75 (1H, dd, *J* = 2.8, 8.7 Hz), 7.10 (1H, d, *J* = 8.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.43, 24.81, 24.89, 28.26, 36.84, 37.40, 38.45, 43.04, 53.31, 55.04, 112.69, 114.26, 126.31, 130.26, 136.07, 158.45, 213.90. **15e**: ^{1}H NMR δ 0.69 (3H, d, *J* = 6.5 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 1.55 - 1.80 (3H, m), 2.00 - 2.20 (2H, m), 2.65 - 2.85 (4H, m), 3.25 (1H, dd, *J* = 10.8, 19.4 Hz), 3.80 (3H, s), 6.68 (1H, d, *J* = 2.8 Hz), 6.80 (1H, dd, *J* = 2.8, 9.8), 7.25 (1H, d, *J* = 9.8 Hz); ^{13}C NMR δ 23.80, 24.0, 25.02, 25.79, 27.21, 30.67, 44.92, 47.70, 55.08, 67.66, 112.71, 113.41, 125.61, 128.32, 138.59, 157.74, 210.81.
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(*Received in UK* 22 *May* 1997; *revised* 17 *June* 1997; *accepted* 20 *June* 1997)