COMMUNICATION

Oxymercuration of 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one: explanation of stereoselectivity

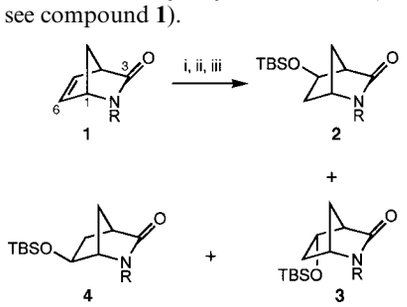
Christopher F. Palmer *[a] **and Ray McCague**[b]

[a] *Chiroscience R & D Ltd and* [b] *Chirotech Technology Ltd, Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE. E-mail: chrispalmer@chiroscience.com*

Received (in Cambridge) 20th July 1998, Accepted 11th August 1998

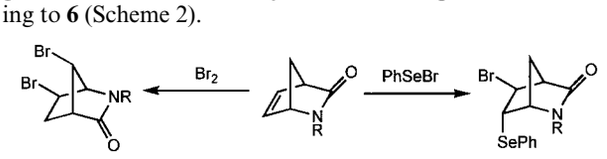
Oxymercuration–demercuration of 2-benzyl-2-azabicyclo-[2.2.1]hept-5-en-3-one with mercuric acetate–sodium borodeuteride showed that the 6-*exo* alcohol arises from *endo*-addition of mercury to the double bond rather than *exo*-addition due to the soft nature of the electrophile leading to the stable cationic intermediate.

The bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one **1** (R = H) is a versatile synthon for the synthesis of carbocyclic nucleosides.[1] As part of ongoing studies into the synthesis of potential carbocyclic nucleoside precursors from the single isomer lactam[2] we were interested in the synthesis of the 5-*exo* alcohol **2** (R = H), a potential precursor of 2′-deoxycarbocyclic nucleosides.[3] Thus we were able to prepare **2** (R = Bn) in a non-selective manner, together with the 6-*exo* **4** and 5-*endo* **3** alcohols in a ratio of 2:2:1 by oxymercuration[4] (Scheme 1, for numbering see compound **1**).



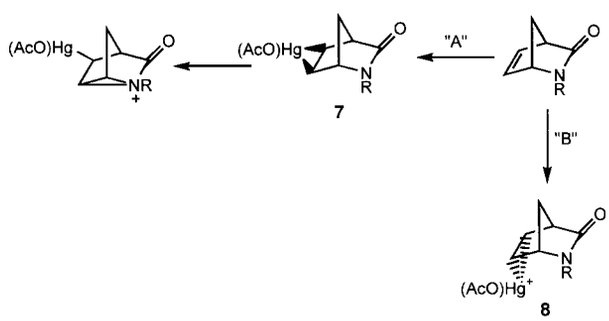
Scheme 1 *Reagents*: i, $Hg(OAc)_2$, aq. THF; ii, $NaBH_4$; iii, TBSCl–imidazole.

Previous work has shown that two distinct reaction pathways occur during electrophile addition to the bicyclic lactam.[5] Thus bromination gives rise to the rearranged dibromide **5** *via exo*-addition of bromine and trapping of the incipient bromonium ion by the amide nitrogen. In contrast phenylselenyl addition gives rise almost exclusively to *endo* electrophile addition leading to **6** (Scheme 2).



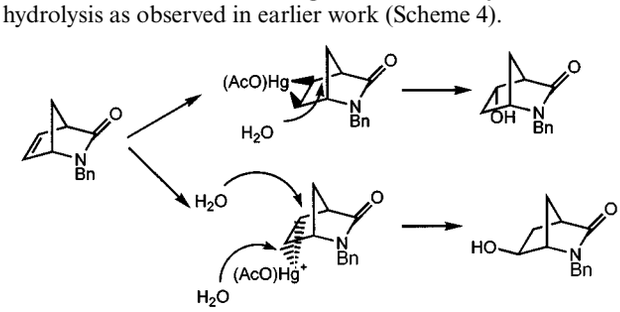
Scheme 2 Electrophile addition to 2-azabicyclo[2.2.1]hept-5-en-3-one.

We reasoned that production of the 5-*exo* alcohol would require a reaction analogous to that observed for phenylselenylation, *i.e. endo* electrophile addition followed by regioselective ring opening of the resultant mercuranium species. This would not be totally unexpected since some related work by Carroll[6] implicates a single *endo* mercuranium species. While the formation of the 5-*exo* and 5-*endo* alcohols be can explained by the selective opening of the *exo*/*endo* mercuranium ions **7**,**8**, the origin of the 6-*exo* alcohol **4** (R = H), a potential intermediate for the synthesis of carbocyclic 3′-deoxycarbocyclic nucleosides,[7] is not clear since it can arise from either rearrangement *via* nitrogen participation (pathway A) with inversion of stereochemistry at C-1 and C-4 or nucleophilic attack at C-6 (pathway B) with retention of stereochemistry (Scheme 3).



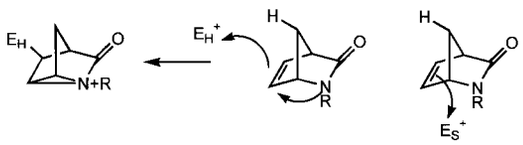
Scheme 3 Possible routes to the 6-*exo* alcohol.

In this paper evidence to determine which of these pathways was responsible for the formation of **4** is presented. A labelling study was carried out in which demercuration with sodium borodeuteride was expected to show the final location of the mercury. Oxymercuration–demercuration followed by silylation was carried out as previously described to give the silyl ethers **2**–**4**.[4,6] Extensive ^{1}H NMR studies on each of the compounds determined the location of the deuterium. The key feature in the spectrum of the 6-*exo* alcohol was the complete absence of any deuterium at C-7 as the large geminal coupling H-7_{syn}/H-7_{anti} was still present. Instead deuterium was present at C-5 in a 6:5 ratio of *exo*:*endo*, possibly as a result of a dissociation of the mercury–carbon bond into a planar cation, thus ruling out pathway "A" and indicating that the most likely pathway was "B". These results are consistent with a mechanism involving the formation of an energetically preferred *endo*-acetoxy mercuranium species† which then undergoes direct non-selective nucleophile ring opening with water, a reaction analogous to that observed in the phenylselenylation of the *N*-tosyl lactam **1** (R = Ts). The consequence of this is that no C-7 deuteration is seen and hence both the 5-*exo* and 6-*exo* alcohol arise from a common *endo* mercuranium species followed by non-selective hydrolysis as observed in earlier work (Scheme 4).



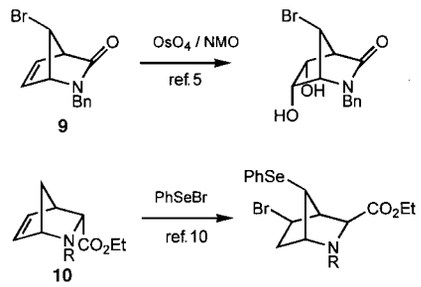
Scheme 4 Proposed mechanism of oxymercuration of 2-azabicyclo-[2.2.1]hept-5-en-3-one.

The preferred *endo*-mercuration of the lactam can be explained by analogy with our previous results.[5] In general hard electrophiles such as bromine prefer to add *exo* where the resultant cation can be stabilized by participation of the nitrogen lone pair. In contrast, soft electrophiles, which in general are more bulky and produce more stable cations, prefer to add to the *endo* face of the double bond as a result of the steric hindrance from H-7_{anti} (Scheme 5).[8] Nucleophilic ring opening of the resultant cation is then determined by electronic effects.



Scheme 5 Modes of electrophile addition to 2-azabicyclo[2.2.1]hept-5-en-3-one.

In cases where the steric factors outweigh electronic effects these preferred pathways can be reversed as evidenced by the dihydroxylation of the 7-*anti*-bromide **9**[9] and the phenylselenylation of the azanorbornene carboxylate **10** (Scheme 6).[10] In



Scheme 6 Reversal of electrophile addition.

the former case a bulky group prevents the preferred mode of addition to the double bond as previously observed for lactam **1** (R = H)[11] with the result that the least favoured addition is observed.

In contrast the *N*-acyl 2-azanorbornene **10**,[10] unlike the unsubstituted system of Carroll[6] which appears to more closely mimic our system, appears to favour an *exo*-seleniranium species leading to rearrangement as a result of steric constraints on the *endo* face due to the carboxylate.

In conclusion we have shown by a deuterium labelling that a similar reaction pathway to that previously observed for phenylselenylation, where external nucleophilic attack follows electrophile addition, occurs during oxymercuration of 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-ones. Thus selection of the desired enantiomer of the lactam will enable alcohols of defied stereochemistry to be produced.

Experimental

Preparation of silyl ethers 2, 3 and 4

A solution of 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one **1** (R = Bn) (4.68 g, 23.5 mmol) in THF (25 ml) was added dropwise over 20 minutes to a stirred suspension of mercuric acetate (7.58 g, 23.92 mmol) in 1 : 1 THF–D_2O (160 ml) at 0 °C under N_2. The resulting bright yellow mixture was stirred under N_2 for 1 h, allowed to warm to ambient temperature and stirred for 4 days at which point TLC (eluent 1 : 1 Et_2O–pentane) showed no starting material to be present. The reaction mixture was cooled to 0 °C. Sodium borodeuteride (1 g, 23.88 mmol) was added in small portions over 10 minutes—an immediate colour change was accompanied by the precipitation of mercury. The aqueous layer was decanted off the mercury and extracted with ethyl acetate (5 × 100 ml). The organic layers were combined, washed with 1 : 1 saturated aqueous $NaHCO_3$–brine (3 × 50 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was partially purified by filtration through a silica pad (EtOAc) to give the *mixed alcohols* (2.00 g, 40%).

A solution of the *alcohols* (2.0 g, 9.2 mmol), *tert*-butyldimethylsilyl chloride (1.84 g, 12.21 mmol), and imidazole (1.33 g, 19.54 mmol) in dry DMF (10 ml) was stirred at RT under N_2 for 18 h. The solution was partitioned between diethyl ether (200 ml) and saturated aqueous ammonium chloride (50 ml). The aqueous layer was separated and extracted with diethyl ether (2 × 200 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography [silica, 2 : 1 then 1 : 1 light petroleum (bp 40–60 °C)–diethyl ether] to give the silyl ethers.

Representative ^{1}H NMR spectral data for the 5-*exo*, 6-*exo* and 5-*endo* silyl ethers (**2**, **3** and **4**) are shown below (corresponding data for the non-deuterated compounds are shown in square brackets). Note that the yields quoted are based on the mixed alcohols.

5-*exo* 2. Yield 0.60 g, 20%; δ_H($CDCl_3$, 300 MHz) 4.22 (1H, app. br dd, contains $J_{5\text{-}endo\text{–}6\text{-}endo}$ 6.6 Hz, $J_{5\text{-}endo\text{–}7\text{-}anti}$ 1.3 Hz, H-5-*endo*) [(1H, ddd, $J_{5\text{-}endo\text{–}6\text{-}endo}$ 6.6 Hz, $J_{5\text{-}endo\text{–}7\text{-}anti}$ 1.3 Hz, $J_{5\text{-}endo\text{–}6\text{-}exo}$ 2.2 Hz, H-5-*endo*)], 2.02 (2.5H, app. dd contains $J_{6\text{-}endo\text{–}6\text{-}exo}$ 13 Hz, $J_{6\text{-}endo\text{–}5\text{-}endo}$ 6.6 Hz, H-6-*endo*), 1.94 [(3H, m, H-7-*anti*, H-7-*syn*, H-5-*exo*)], 1.46 (0.5H, br m, H-6-*exo*) [(1H, ddd, $J_{6\text{-}exo\text{–}6\text{-}endo}$ 13 Hz, $J_{6\text{-}exo\text{–}5\text{-}endo}$ 2.2 Hz, $J_{6\text{-}exo\text{–}4}$ 2.1 Hz, H-6-*exo*)].

6-*exo* 4. Yield 0.20 g, 6.5% (see also ref. 4); δ_H 3.76 (1H, br dd, $J_{6\text{-}endo\text{–}5\text{-}endo}$ 6.6 Hz, $J_{6\text{-}endo\text{–}5\text{-}exo}$ 2.2 Hz, H-6-*endo*) [(1H, ddd, $J_{6\text{-}endo\text{–}5\text{-}endo}$ 6.6 Hz, $J_{6\text{-}endo\text{–}5\text{-}exo}$ 2.2 Hz, H-6-*endo*)], 1.98 (0.5H, br d, $J_{5\text{-}endo\text{–}5\text{-}exo}$ 13 Hz, H-5-*exo*), [(1H, dd, $J_{5\text{-}endo\text{–}5\text{-}exo}$ 13 Hz, $J_{5\text{-}endo\text{–}6\text{-}endo}$ 6.6 Hz, H-5-*endo*)], 1.50 (0.5H, br m, H-5-*exo*) [(1H, ddd, $J_{6\text{-}exo\text{–}6\text{-}endo}$ 13 Hz, $J_{5\text{-}exo\text{–}H\text{-}4}$ 4.0 Hz, $J_{5\text{-}exo\text{–}6\text{-}endo}$ 2.2 Hz, H-5-*exo*)].

5-*endo* 3. Yield 0.52 g, 17%; δ_H($CDCl_3$) 4.52 (2H, m including $J_{5\text{-}exo\text{–}4}$ 4.2 Hz and $J_{5\text{-}exo\text{–}6\text{-}endo}$ 2.9 Hz, H-5-*exo* and CH_2Ph) [(2H, m including $J_{5\text{-}exo\text{–}6\text{-}exo}$ 8 Hz, $J_{5\text{-}exo\text{–}4}$ 4.2 Hz and $J_{5\text{-}exo\text{–}6\text{-}endo}$ 2.9 Hz, H-5-*exo* and CH_2Ph)], [1.94 (1H, ddd, $J_{6\text{-}exo\text{–}6\text{-}endo}$ 13 Hz, $J_{6\text{-}exo\text{–}5\text{-}exo}$ 8 Hz and $J_{6\text{-}exo\text{–}1}$ 2.4 Hz, H-6-*exo*)], 1.84 (1H, dddd, $J_{7\text{-}anti\text{–}7\text{-}syn}$ 9.7 Hz, $J_{7\text{-}anti\text{–}1}$ 2.2 Hz, $J_{7\text{-}anti\text{–}6\text{-}endo}$ 3.7, $J_{7\text{-}anti\text{–}4}$ 1.6 Hz, H-7-*anti*), 1.24 (1H, br s, H-6-*endo*) [(1H, ddd, $J_{5\text{-}endo\text{–}5\text{-}exo}$ 13 Hz, $J_{6\text{-}endo\text{–}5\text{-}exo}$ 2.9 Hz, $J_{6\text{-}endo\text{–}7\text{-}anti}$ 3.7 Hz, H-6-*endo*)].

Acknowledgements

We wish to thank Dr Vladamir Sik (University of Exeter) for his help in the determination of the structures of the deuterated lactams.

Notes and references

† Note that an alternative reduction pathway *via* an epoxide type intermediate can be discounted since this would be expected to give the C-7 alcohol and there is no evidence for such a species in crude reaction mixtures.

1 N. Katagiri, M. Muto and C. Kaneko, *Tetrahedron Lett.*, 1989, **30**, 1645; J. Chen, M. Grim, C. Rock and K. Chan, *Tetrahedron Lett.*, 1989, **30**, 5543; R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17; M. E. Jung and H. Rhee, *J. Org. Chem.*, 1994, **59**, 4719; N. Katagiri, M. Takebayashi, H. Kokufuda, K. Kanehira and M. Torihara, *J. Org. Chem.*, 1997, **62**, 1580.

2 S. J. C. Taylor, A. G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. Evans, *J. Chem. Soc.*, *Chem. Commun.*, 1990, 1120; S. J. C. Taylor, R. McCague, R. Wisdom, C. Lee, K. Dickson, G. Ruecroft, F. O'Brien, J. Littlechild, J. Bevan, S. M. Roberts and C. Evans, *Tetrahedron: Asymmetry*, 1993, **4**, 1117; C. F. Palmer, R. McCague, G. Ruecroft, S. Savage, S. J. C. Taylor and C. Ries, *Tetrahedron Lett.*, 1996, **37**, 4601.

3 B. L. Bray, S. C. Dolan, B. Halter, W. Lackey, M. B. Schilling and D. J. Tapolczay, *Tetrahedron Lett.*, 1995, **36**, 4483; C. D. Maycock, M. T. Barros, A. G. Santos and L. S. Godinho, *Tetrahedron Lett.*, 1993, **34**, 7985; A. D. Borthwick, A. J. Crame, A. M. Exall and G. G. Weingarten, *Tetrahedron Lett.*, 1994, **35**, 7677.

4 C. F. Palmer, B. Webb, S. Broad, S. Casson, R. McCague, A. J. Willetts and S. M. Roberts, *Bioord. Med. Chem. Lett.*, 1997, **7**, 1299.

5 C. F. Palmer, K. P. Parry, S. M. Roberts and V. Sik, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 1021.

6 F. I. Carroll, P. Abraham, S. Chemburkar, X.-C. He, S. W. Mascarella, Y. W. Kwon and D. J. Triggle, *J. Med. Chem.*, 1992, **35**, 2184.

7 Y. F. Shealy and C. A. O'Dell, *Tetrahedron Lett.*, 1969, 2231; C. F. Palmer, K. P. Parry and S. M. Roberts, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 484.

8 A similar rationale has been proposed previously to explain the products of phenylselenylation of the *N*-tosyl lactam **1** (R = Ts)[5] and more recently the iodination of some ring opened analogues: A. Toyota, Y. Ono and C. Kaneko, *Tetrahedron Lett.*, 1995, **36**, 6123.

9 W. C. Faith, C. A. Booth, B. M. Foxman and B. B. Snider, *J. Org. Chem.*, 1985, **50**, 1983.

10 M. B. Hursthouse, K. M. Abdul Malik, D. E. Hibbs, S. M. Roberts, A. J. H. Seago, V. Sik and R. Storer, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 2419.

11 R. C. Cermak and R. Vince, *Tetrahedron Lett.*, 1981, **22**, 2331.

Communication 8/05640D