Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 4323–4327
Tetrahedron Letters

Synthesis of 8-substituted bicyclo[3.2.1]octane-6-carboxylic acids and anti-convulsant properties of the corresponding amides

J. A. Miller,[a,*] J. Harris,[b] A. A. Miller,[c] G. M. Ullah[a] and G. M. Welsh[a]

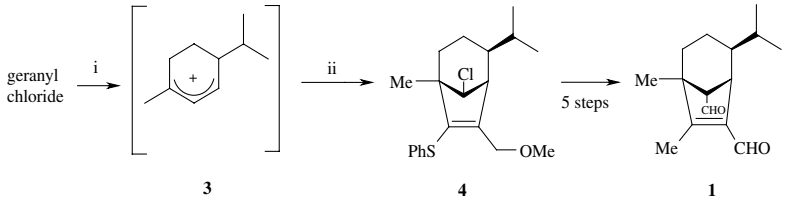
[a]*Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK*
[b]*School of Chemistry, University of St. Andrews, Fife KY16 9ST, Scotland, UK*
[c]*Department of Pharmacology, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK*

Received 1 October 2003; revised 25 March 2004; accepted 2 April 2004

Abstract—Novel 8-substituted bicyclo[3.2.1]octane-6-carboxylic acids have been made via [3+2]cycloaddition to alkyne **2**. A number of the corresponding amides are anti-convulsant in mice.

Sometime ago, one of us reported a novel route to bicyclo[3.2.1]octane derivatives via the zinc chloride-mediated [3+2]cycloaddition of cyclohex-2-enyl chlorides to alkynes.[1] This method was extended to mono- and bis-sulfenyl alkynes,[2] and then applied to a synthesis of 4-*epi*-helminthosporal **1**.[3] The first step in this synthesis was a highly regio- and stereoselective cycloaddition of the phenylsulfenyl alkyne **2** to the allylic intermediate **3**, generated in situ from geranyl chloride and zinc chloride,[4] to give bicyclo[3.2.1]oct-6-ene adduct **4**—see Scheme 1. (All reported compounds are racemates, but are shown as having the bridge 'up', on the *exo* face).

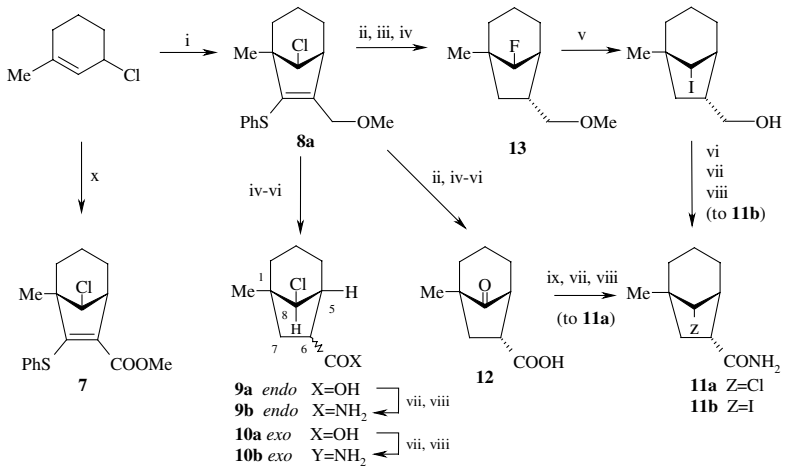
One of the interesting properties of the bicyclo-[3.2.1]octane skeleton is that it is fairly rigid and can therefore subtend two or more ligands in a reasonably predictable three-dimensional relationship—a feature of potential value to medicinal chemists, particularly in the search for selectivity. Indeed, our methodology has recently been applied in this way to prepare novel opioid antagonists.[5] It was also envisioned that the same approach should allow access to compounds such as **5**, in which X, Y, and Z are variously H, NH_2, and/or COOH, and which we regarded as constrained and relatively lipophilic versions of neurotransmitters such as glutamate, aspartate and gamma amino butyric acid (GABA). The recent literature shows an intense interest in this subject[6] although examples based on the bicyclo[3.2.1]octane skeleton are relatively rare—for example, the work of Meltzer et al.[6] who have focussed on 2-carboxy and 3-aryl groups as ligands. In order to prepare bicyclic amino acids **5**, it was judged that, in general, separate methodology would be needed to



Scheme 1. Reagents and conditions: (i) $ZnCl_2$, CH_2Cl_2, 0–20 °C; (ii) PhSC≡CCH$_2$OMe **2** (85%—two steps).

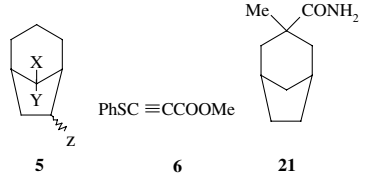
Keywords: [3+2]Cycloaddition; Bicyclo[3.2.1]octane-6-carboxylic acids/amides; Anti-convulsant activity.
* Corresponding author. Address: 18 South View Avenue, Macclesfield, Cheshire SK11 9RZ, UK. Tel.: +44-1625-610215; e-mail addresses: allison@miller4444.freeserve.co.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.007



Scheme 2. Reagents and conditions: (i) $ZnCl_2$, PhSC≡CCH_2OMe **2**, CH_2Cl_2 0–20 °C, (75–90%) (Ref. 8); (ii) $Hg(ClO_4)_2$, aq DME (64%) (Ref. 8); (iii) DAST, CH_2Cl_2, −50 to 20 °C, (65%) (Ref. 8); (iv) Raney Ni, EtOH (96%); (v) $AlCl_3$, NaI, $MeCN/CH_2Cl_2$ (30–62%); (vi) CrO_3, H_2SO_4, aq acetone (95%); (vii) $SOCl_2$, Δ; (viii) NH_3 (90%—two steps); (ix) $NaBH_4$, MeOH, 20 °C (8-*endo* alcohol) 60% (with <20% 8-*exo* alcohol); (x) $ZnCl_2$, PhSC≡CCOOMe **6**, CH_2Cl_2, 0–20 °C (10–30%).

introduce each amino and carboxy ligand. The former has already been achieved through the synthesis of a series of 8-aminobicyclo[3.2.1]octanes, several of which were anti-viral agents against influenza and respiratory syncytial viruses.[7] In this paper, we initially address the synthesis of 8-substituted bicyclooctane-6-carboxlyates via [3+2]cycloaddition and report that a number of the corresponding primary amides have anti-convulsant properties.



5 **6** **21**

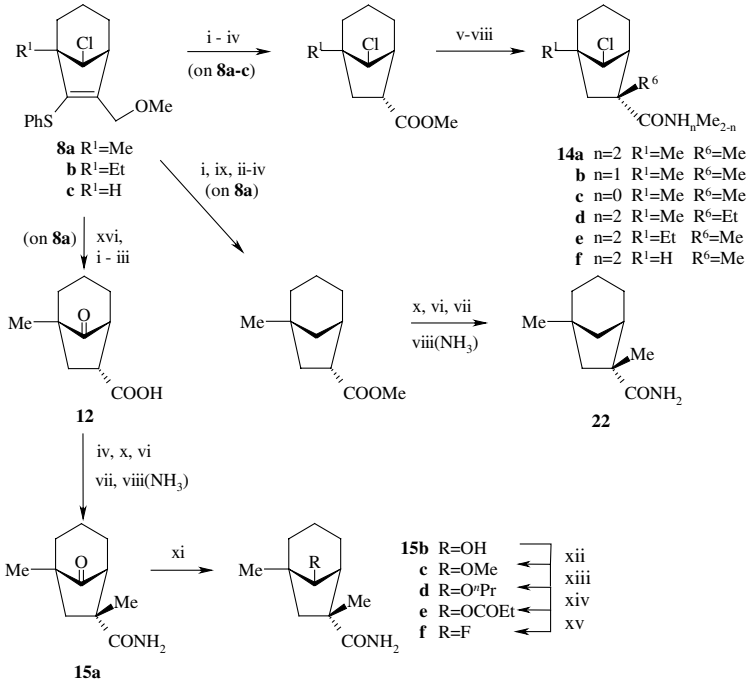
In principle, the most direct [3+2]cycloaddition route to bicyclo[3.2.1]octane-6-carboxylates would involve a simple alkyne component like methyl propiolate, but early failures with simple propiolates indicated that they did not have the desired donor–acceptor properties. The subsequent discovery[2] that phenylsulfenyl alkynes were superior [3+2]cycloaddition partners (not only improving yields, but also controlling the regiochemistry when nonsymmetrical allyl cations were involved) suggested that the phenylsulfenyl propiolate **6** would be worth trying. In practice, however, with 3-chloro-1-methylcyclohexene (which usually contained 10–15% of the allylic isomer 3-chloro-3-methylcyclohexene—both of which give the same allyl cation[8]) yields of adduct **7** were both low and variable, and deemed not good enough for the first key intermediate in our proposed synthesis. With this background, we reverted to the phenylsulfenyl propargyl ether **2** that had served our purpose so well in the helminthosporane work[3] and in the synthesis of bicyclic α-methylene ketones.[8] The syntheses of our initial targets, acids **9a** and **10a**, from the [3+2]-cycloadduct **8a**, are set out in Scheme 2 and structures were only assigned to **9a** and **10a** after extensive proton NMR studies. It was expected that the *endo* chloride configuration at the bridge C-8 would be retained through the conversion of **8a** into the bicyclic acids, and this was confirmed for both **9a** and **10a** by doublets with ^3J 5.5 Hz at δ 4.09 and 4.00 ppm, respectively.[9] Connectivity in the acid **9a** was established via 2D COSY, and NOEDS revealed strong enhancements at H-6b and H-7b when H-8 was irradiated, and at H-6b, H-7a, and H-8 when H-7b was irradiated. Lipophilic carboxylic acids and their simple amides both have precedent as anti-convulsants,[10] and therefore both series were tested in the standard mouse electro-shock model used as our basic screen for anti-convulsant activity. We found that neither acid **9a** or **10a** was significantly active. However, the corresponding primary amide (initially made as a mixture of epimers at the 6-position) had modest activity (ED_{50} 80 mg/kg—where ED_{50} is the dose of drug observed to protect 50% of the animals). When the C-6 epimers were tested individually, activity was found to reside largely in the *endo* carboxamide **9b** and thereafter we therefore tested all amides in order to establish SAR.

The syntheses of **9**–**11** (Scheme 2) generally used conventional methodology, as illustrated by the route to **11a** via the ketoacid **12**, regarded as key because it is, in principle, a ready precursor for structures **5**. However, one unexpected observation was that the 8-fluoroether **13** (made from **8a** via mercuric perchlorate-mediated hydrolysis,[8] treatment with DAST,[11] and then with Raney Nickel) underwent not only the expected *O*-demethylation with aluminum chloride/sodium iodide. To our surprise, the 8-*endo* fluoride group was partially lost under these conditions and the proton NMR signals for the CHF group were replaced by an broad singlet (sometimes resolved into a doublet with $^3J < 1.0$ Hz) at δ 4.24 ppm, which we initially assigned to an 8-CHX group with 8-*exo* geometry.[9] It was only when the corresponding 8-*exo* chloride **11a** became available that we were able to compare the proton NMR spectrum of **11a**

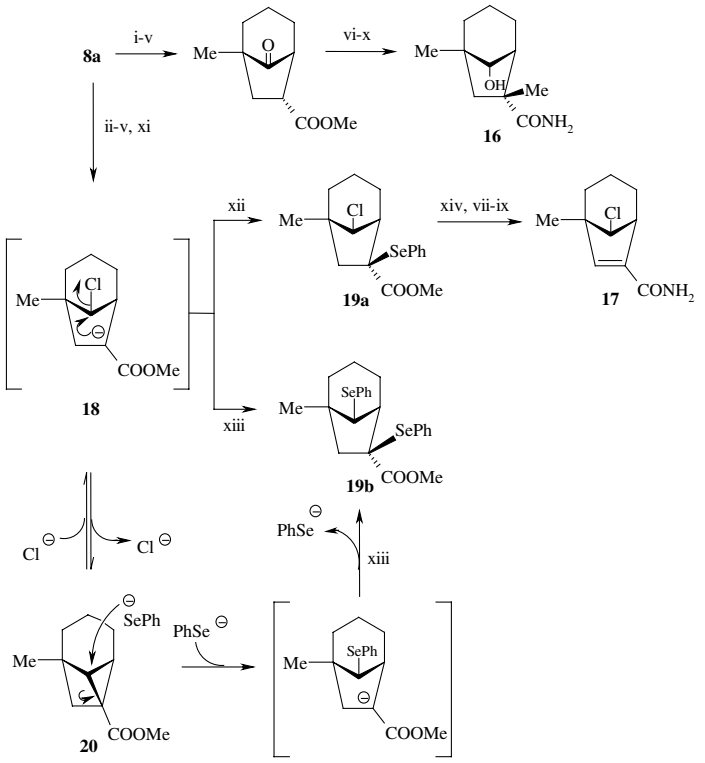
with that of the above unassigned amide. They were virtually identical, except that the bridge proton of the latter was about 0.30 ppm deshielded compared with the corresponding CHCl proton in **11a**—as would be expected for an 8-*exo* iodide, such as **11b**.[12] The $AlCl_3$–NaI combination is a known, but not widely used, reagent for ether cleavage,[13] but we are not aware of such a 'contra-thermodynamic' fluoride to iodide conversion with this reagent, and we did not observe the analogous exchange with any 8-*endo* chloride under ether cleavage conditions. It was also interesting that the methyl ester intermediate in the 8-*exo* iodide series, leading to **11b**, was completely resistant to α-methylation. Since this was routinely achieved with all the other esters we tried, it seems that the bulky *exo* iodo group is responsible, probably because it blocks access to the *exo* face of the ester enolate.

The preparation of **11a** and **11b**, each with an 8-*exo* halogen, allowed us to explore the effect of bridge geometry on anti-convulsant activity, but, to our surprise, both were totally inactive. Thereafter, the focus was on compounds bearing alkyl groups both at the 6-position and on the carboxamide, all synthesized via adduct **8a**, as reported in Scheme 3. In the sequence leading to **14a** and **14d**, alkylation of the intermediate ester enolate occurred from the *exo* face, as would be expected for a bridged bicyclic system. Compound **14a**, bearing a quaternary methyl group at the 6-position became the new lead with an oral ED_{50} of 51 mg/kg, and it was quickly established that *N*-methylation to give **14b–c** was detrimental to activity. Moreover, it was also found that **14d** was inactive, suggesting that further bulk at C-6 would not be tolerated. In order to examine the effect of varying substituents at the 1-position, **8b** and **8c** were the start points, leading to the amides **14e** and **14f**, which were found to be modestly active and inactive, respectively, again suggesting that a methyl ligand is optimal. At this point, the major remaining SAR issues concerned the substitution at C-8, the bridge carbon. The activity of early lead **11a**, followed by the more potent **14a**, both of which were *endo* at C-8, was in stark contrast to the inactivity of the *exo*-substituted derivatives **11a** and **11b**, and indicated that further C-8 *endo* compounds should be made—see **15a–f** in Scheme 3. Of these, the only two found to be weakly active were the methyl ether **15c** and the fluoride **15f** (the latter only against chemically-induced seizures). We were unable to prepare a satisfactory sample of the analogous bromide.

For completeness, the C-8 *exo* alcohol **16** and the unsaturated carboxamide **17** were prepared, as in Scheme 4, and the latter was found to be weakly active. The last step in the synthesis of **16** required a bulky source of hydride, such as L-selectride, in contrast to the earlier reduction of **15a** to give **15b**, which was achieved with sodium borohydride. An interesting feature of the synthesis of **17** was that the presumed enolate intermediate **18** gave the expected α-phenylselenyl ester **19a** when phenylselenyl chloride was used. The PhSe group was presumed on chemical grounds to be *exo* and this was confirmed by the 8-CHCl doublet (^3J 5.5 Hz) being hugely deshielded (by 0.85 ppm, to δ 4.72 ppm) by the PhSe group—an effect only explicable with the geometry assigned to **19a**. However, when diphenyldiselenide was



Scheme 3. Reagents and conditions: (i) Raney-Ni, EtOH (62–96%); (ii) $AlCl_3$, NaI, $MeCN/CH_2Cl_2$ (30–62%); (iii) CrO_3, H_2SO_4, aq acetone (85–95%); (iv) MeI, K_2CO_3, acetone (92–96%); (v) LDA, R^6I, THF (61–85%); (vi) NaOH, EtOH (85–92%); (vii) $SOCl_2$, Δ; (viii) NH_3, $MeNH_2$ or Me_2NH (85–95%—two steps); (ix) Na, EtOH (32%); (x) LDA, MeI, THF (82–88%); (xi) $NaBH_4$, MeOH, (62%); (xii) NaH, MeI, THF (82%); (xiii) NaH, *n*-PrI, THF (73%); (xiv) EtCOCl, py (85%); (xv) DAST, CH_2Cl_2 (65–68%); (xvi) $Hg(ClO_4)_2$, aq DME (64%) (Ref. 8).



Scheme 4. Reagents and conditions: (i) $Hg(ClO_4)_2$, aq DME (64%) (Ref. 8); (ii) Raney Ni, EtOH (94%); (iii) $AlCl_3$, NaI, $MeCN/CH_2Cl_2$, rt (62%); (iv) CrO_3, H_2SO_4, aq acetone (58%); (v) MeI, K_2CO_3, acetone (100%); (vi) MeI, LDA, 80 °C (98%); (vii) NaOH, EtOH, Δ (73%); (viii) $SOCl_2$, Δ (ix) NH_3 (35–75%—two steps); (x) L-selectride, THF (43%); (xi) LDA, THF–HMPA; (xii) PhSeCl (63%); (xiii) PhSeSePh (38% of **19b**); (xiv) H_2O_2, CH_2Cl_2 (65%).

employed, the major product (38%) was the bis-phenylselenated compound **19b**, in which the bridge chloride had been substituted, with retention of configuration. There is some precedent for this type of enolate chemistry in bridged and other bicyclic systems,[14] and a speculative explanation is presented in Scheme 4. It is envisaged that the initial enolate either reacts with $(PhSe)_2$ to give **19a**, as above, or quenches internally with displacement of chloride to give the tricyclo-[3.2.1.$0^{6,8}$]octane **20**, which can ring-open with the phenylselenide anion to regenerate the bicyclo-[3.2.1]skeleton as an enolate. This can then be phenylselenated to produce **19b**. In principle, this type of enolate chemistry may offer a general route to functional group exchange at C-8 under basic conditions, thus complementing Lewis acid-mediated exchanges of chlorine reported for N_3,[7] OH,[5] and F.[8]

The broad SAR across the amide series suggests that overall bulk is a major determinant of activity, and that orientation of ligands such as carboxamide, hydroxyl, and/or halogen is also important. The closest analogy that we are aware of comes from a Sanofi patent,[15] in which compound **21** was reported very briefly as the most potent in a low-activity series of bicyclo-[3.2.1]octane-3-carboxamides. In our series, carboxamide **14a** thus remained the best compound and its oral activity was confirmed in further studies of chemical (leptazole) induced seizures in mice. The *endo* chlorine at C-8 is clearly contributing to activity (not only is the *exo* isomer **11a** inactive, but so is the amide **22**, in which the bridge is unsubstituted) and it might be worth adding a chlorine at C-8 in **21**—a substitution which would, in principle, be facile. On the down side, **14a** and its close congeners also seemed to have depressant effects on mice at two to three times ED_{50}, and this contributed to loss of interest in the series, particularly as Wellcome had a clearly superior compound (Lamictal) in clinical development as an anti-convulsant at the time.

Acknowledgements

The authors gratefully acknowledge data on mouse models of epilepsy supplied by Dr Rob O'Donnel, Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, UK, and by Dr Bob Ferris, Burroughs Wellcome Co., Research Triangle Park, North Carolina, USA, and colleagues.

References and notes

1. Gray, B. D.; McMillan, C. M.; Miller, J. A.; Moore, M. *Tetrahedron Lett.* **1987**, *28*, 235–238.
2. Gray, B. D.; McMillan, C. M.; Miller, J. A.; Ullah, G. M. *Tetrahedron Lett.* **1987**, *28*, 689–692.
3. Gray, B. D.; Miller, J. A. *J. Chem. Soc., Chem. Commun* **1987**, 1136–1137.
4. Gray, B. D.; Miller, J. A. *J. Chem. Res. (S)* **1987**, 206–207.

5. Miller, J. A.; Pope, S. A.; Riddall, D. R.; Ullah, G. M.; Welsh, G. M. *Tetrahedron Lett.* **2003**, *44*, 8411–8415.
6. This area of research has been of prolific interest over the last 20 years or so. For an overview of earlier work see: Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057–2066; For recent, illustrative examples of bicyclic analogues see Kozikowski, A. P.; Araldi, G. L.; Flippen-Anderson, J.; George, C.; Pshenichkin, S.; Surina, E.; Wroblewski, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 925–930 (bicyclo[3.2.0]); Ezquerra, J.; Yruretagoyena, B.; Avendao, C.; De la Cuesta, E.; Gonzalez, R.; Prieto, L.; Pedregal, C.; Espada, M. *Tetrahedron* **1995**, *51*, 3271–3278; Conti, P.; De Amici, M.; Joppolo di Ventimiglia, S.; Stensbøl, T. B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; De Sarro, G.; Bruno, G.; De Micheli, C. *J. Med. Chem.* **2003**, *46*, 3102–3108 (bicyclo[3.3.0]); Tellier, F.; Acher, F.; Brabet, I.; Pin, J.-P.; Azerad, R. *Bioorg. Med. Chem.* **1998**, *6*, 195–208; Kozikowski, A. P.; Steensma, D.; Araldi, G. L.; Tückmantel, W.; Wang, S.; Pshenichkin, S.; Surina, E.; Wroblewski, J. T. *J. Med. Chem.* **1998**, *41*, 1641–1650; Axford, L.; Boot, J. R.; Hotten, T. M.; Keenan, M.; Martin, F. M.; Milutinovic, S.; Moore, N. A.; O'Neill, M. F.; Pullar, I. A.; Tupper, D. E.; Van Belle, K. R.; Viven, V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3277–3280 (bicyclo[2.2.1]); Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z.; George, C.; Gonzalez, M. D.; Madras, B. K. *J. Med. Chem.* **2000**, *43*, 2982–2991 (bicyclo[3.2.1]).
7. Miller, J. A.; Ullah, G. M.; Welsh, G. M.; Hall, A. C. *Tetrahedron Lett.* **2001**, *42*, 7503–7507.
8. Miller, J. A.; Ullah, G. M.; Welsh, G. M.; Mallon, P. *Tetrahedron Lett.* **2001**, *42*, 2729–2731.
9. In 1,8-di-substituted bicyclo[3.2.1] systems observation of a doublet (^3J 5.0–5.5 Hz) has become an accepted indicator of 8-*endo* geometry in the CHX group. The corresponding 8-*exo* geometry for the CHX group is consistently found to have smaller coupling (^3J 0.5–1.0 Hz).[7,8] For further examples, see: (a) Piers, E.; Britton, E. W.; Geraghty, M. B.; Keziere, R. J.; Kido, F. *Can. J. Chem.* **1975**, *53*, 2838–2848; (b) Piers, E.; Geraghty, M. B.; Smillie, R. D.; Soucy, M. *Can. J. Chem.* **1975**, *53*, 2849–2864.
10. 'The Year's Drug News' 1994 Edition, J. R. Prous, Barcelona, Chapter 9, pp 55–59. This overview is unusual in that it lists the structures of all anti-convulsants on the market or in the clinic.
11. The 8-*endo* fluoride, derived from **8a** via the 8-*endo* alcohol and DAST, was characterized by its diagnostic ABX pattern (dd centred at δ 4.54 ppm, $^2J_{HF}$ 48 Hz; $^3J_{HH}$ 5.5 Hz) for the bridge CHF proton. The same feature was present in the 8-fluoro derivative **13**, thus confirming that reaction of the bridge alcohol with DAST had occurred with retention, and that the 8-*endo* fluoride geometry had only been inverted at C-8 after treatment with $AlCl_3$-NaI.
12. The iodocarboxamide **11b** was not very stable and good analytical data were not obtained. Appropriate analytical and spectroscopic data (NMR and MS) have been obtained for other compounds submitted for anti-convulsant testing.
13. Node, M.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Tetrahedron Lett.* **1984**, *25*, 219–222; Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1983**, *31*, 4178–4180.
14. A close example with a similar explanation has been described for the conversion of 7-chloronorbornan-2-one into 7-methoxynorbornan-2-one, with retention—see Lumb, J. T.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1966**, 400.
15. Boigegrain, R.; Chanu, J.; Simiand, J.; Vernieres, J.-C. *European Patent 130,882 A*, **1985**; (to Sanofi). No indication is given of the geometry of the carboxamide relative to the bridge methylene in **21**.