A New Carbanionic One-Carbon Ring Enlargement-Alkylation of Lactams

Michela Valacchi,*[a] Walter Cabri,*[b] Alessandro Mordini,[a] Arnault De Philippis,[a] Gianna Reginato[a]

[a] Istituto di Chimica dei Composti OrganoMetallici, Dipartimento di Chimica Organica 'U. Schiff', via della Lastruccia 13, 50019 Sesto Fiorentino, Firenze, Italy
Fax +39(055)4573580; E-mail: labormet@unifi.it

[b] Antibioticos, Research & Development, strada Rivoltana km 6-7, 20090 Rodano, Milano, Italy
Fax +39(02)95321134; E-mail: WCabri@antibioticos.it

Received 3 September 2003

Abstract: The lithium-bromine exchange of bicyclic bromo-substituted γ- and δ-lactams has been investigated finding that the lithium intermediates undergo a ring-enlargement reaction eventually leading to the isomeric six- and seven-membered lactams. Interception of the lithium species with electrophiles allows the synthesis of a series of functionalized quinolinones and benzoazepines.

Key words: lactams, rearrangement, carbanions, ring-expansion, quinolines

During our investigations on the use of non-toxic nitrogen ligands in samarium(II)-mediated reactions,[1] we have observed an unusual selectivity in the samarium mediated cyclization of bicyclic bromolactam **1**. In particular, we found that the only 6-membered ring lactam detected in the samarium(II) promoted ring expansion was **4**, in contrast with the corresponding Bu_3SnH promoted radical expansion in which a mixture of compounds **2** and **3** is formed (Scheme 1).[2]

This different behaviour can be attributed either to a different course in the rearrangement of radical **5** or to an anionic pathway via the carbanionic species **6** (Figure 1).[3,4] In order to have a clearer picture, we then decided to compare the Sm(II) mediated process with the ring enlargement of the bromolactam **1**, as well as other 5- and 6-membered lactams, induced by treatment with *tert*-butyllithium, thus hopefully moving towards an anionic pathway. Anionic ring-enlargement processes are well documented[5] indeed even if, under such circumstances, the formation of radical species cannot be completely ruled out.[6]

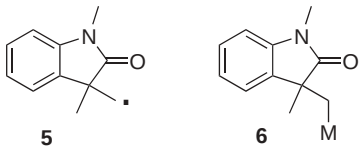
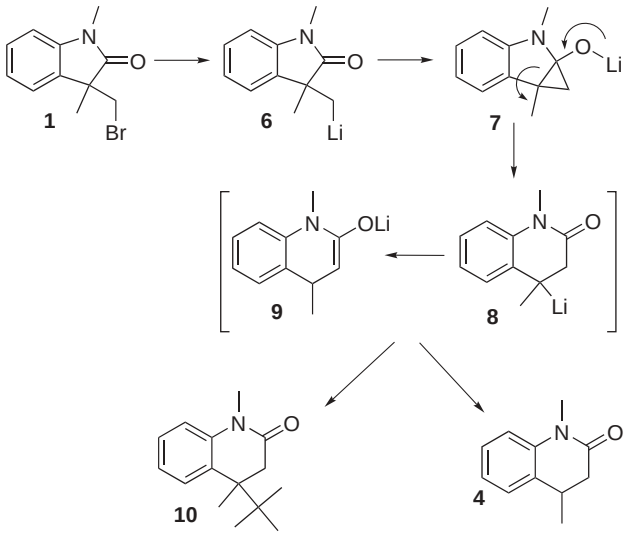
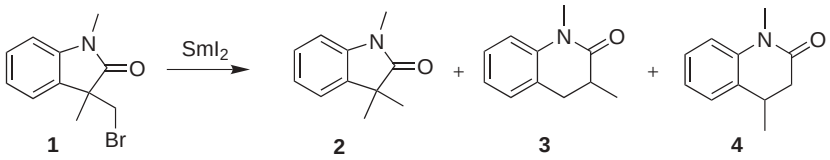


Figure 1

In the first series of experiments, compound **1** was treated with two equivalents *tert*-butyllithium under various experimental conditions[7] as shown in Table 1 (Scheme 2).



Scheme 2



Scheme 1

SYNLETT 2003, No. 13, pp 2025–2028
Advanced online publication: 08.10.2003
DOI: 10.1055/s-2003-42045; Art ID: G23003ST
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: Simon Fraser University Library. Copyrighted material.

Table 1 Reaction of Bromolactam **1** with *tert*-Butyllithium[a] Followed by Quenching with Water

Entry	T [°C]	Solvent	Conversion [%]	Product composition			
				2	**3**	**4**	**10**
1	–45	THF	100	–	–	75	25
2	–18	THF	100	25	–	66	9
3	–45 to 0	Pentane	–	–	–	–	–
4	–45	Pentane: MTBE[b] (9:1)	70	–	–	100	–
5	–45	MTBE[b]	100	14	–	86	–
6	–45	Et_2O	95	14		86	
7	–45[c]	Et_2O	100	27	–	73	–
8	–18	Et_2O	95	20	–	80	–
9	–45	Bu_2O	80	15	–	85	–
10	–45[c]	Ethylal[d]	100	11	–	89	–

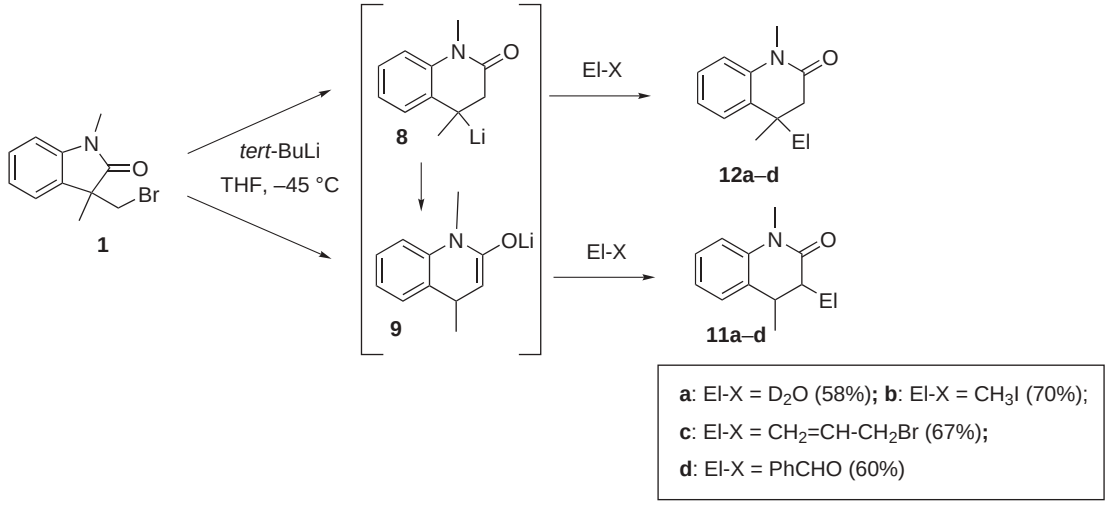
[a] All experiments have been carried out in two hours unless specified.
[b] MTBE = methyl *tert*-butyl ether.
[c] Reaction time: 4 h.
[d] Ethylal = formaldehyde diethylacetal.

The composition of the final reaction mixture is quite similar to that observed in the samarium(II) promoted rearrangement, the only rearranged product being the six-membered ring **4**, although some reduction to **2** also occurs. As shown in Table 1, the reaction is reasonably selective affording the bicyclic lactam **4** as the only rearranged product in ethereal solvents (entry 4–10), while in pentane (entry 3) only starting material is recovered. All ethereal solvents behave similarly, affording small amounts of the debrominated five-membered lactam **2** together with compound **4**, except THF in which no traces of product **2** are found but some alkylated lactam **10** is isolated (entry 1, 2); its formation may be due either to reaction of lithium species **8** with isobutylene[8] (generated by the reaction of the excess *tert*-butyllithium with *tert*-butyl bromide) or to single electron transfer from tertiary benzylic anion **8** to *tert*-butyl bromide, followed by coupling of the two radicals.[9] Changing the temperature, the time or the order of addition of the reagents affects the results to a negligible extent.

Reaction with electrophiles other than water may lead to two products **11** and **12** deriving from the lithium enolate **9** and the benzyl lithium species **8** (Scheme 3), respectively. In order to check this regioselectivity profile, we submitted bromolactam **1** to sequential treatment with *tert*-butyllithium and an electrophilic reagent. Despite the nature of the electrophile, compound **11** is always isolated as the only product in acceptable yields.[10]

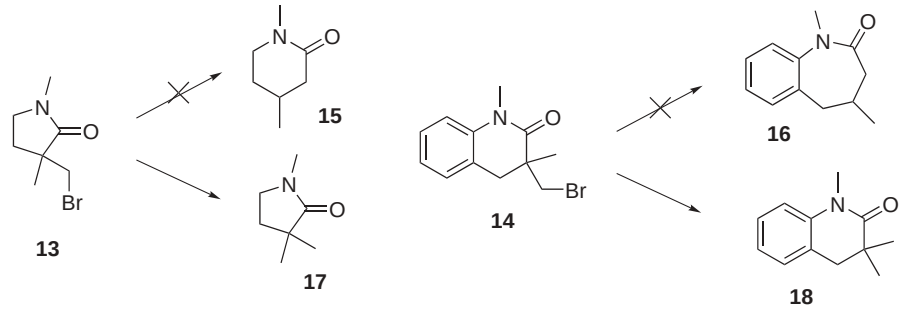
The *tert*-butyllithium promoted ring-enlargement of bromomethyl substituted lactams has strict structural requirements. The isomerization to the benzyllithium intermediate **8** postulated above, implies the presence of a benzofused aromatic ring and the bromomethyl substituent bound to the benzylic position in the starting lactams. Indeed, when we treated bromolactams **13** and **14** with *tert*-butyllithium no ring-enlarged product **15** and **16** were detected and only the reduced lactams **17** and **18** were recovered almost quantitatively (Scheme 4).

On the other hand we were very pleased to find that the bromolactam **19** {readily obtained from N-[(2-chlorophenyl)-methyl-*N*-methylpropanamide via lithiation with LDA and quenching with dibromethane}[11] gave a very clean one-carbon ring expansion to the 7-membered ring lactam **20** after treatment with *tert*-butyllithium and quenching with water (Scheme 5).[12]

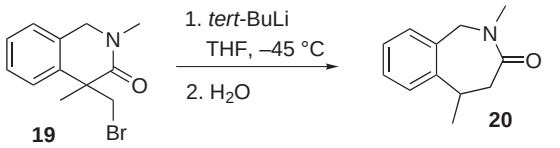


Scheme 3

Downloaded by: Simon Fraser University Library. Copyrighted material.



Scheme 4



Scheme 5

A comparison between lactams **1** and **19** reveals a different behaviour concerning the ring-enlargement/functionalization process. Lactam **1** gives only products deriving from reaction of the lithium enolate when the reaction is conducted at 0 °C. Interestingly, it has been found however that when allylbromide is added at –78 °C, only allyl derivative **12c** is formed, though in moderate yield, thus indicating that the benzyllithium species **8** enolizes to **9** as the temperature is raised to 0 °C. On the other hand the 6-membered ring lactam **19** affords exclusively 7-membered ring lactams **23a**–**c**[13] (Scheme 6) in the investigated temperature range (–78 °C to r.t.) without any contamination from the enolate-derived lactam **24**, although a decrease of the chemical yield is observed at higher temperatures. This regioselectivity profile may be due to a higher stability of the benzyllithium species **21** compared to the analogue **8**.

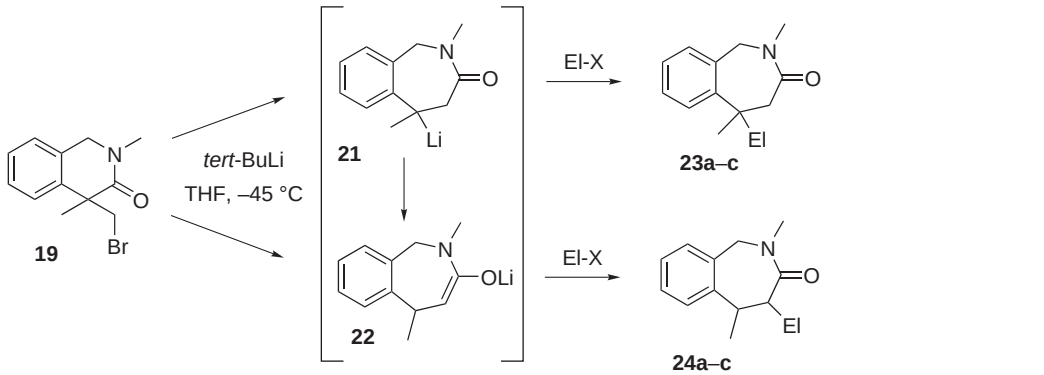
In conclusion, this simple and general approach can be regarded as a new entry into the synthesis of both the quinolinonic and azepinonic structures which are widely found in many compounds endowed with biologically relevant properties (some examples: cilostazol,[14] carteolol,[15] carbostyril,[16] galanthamine,[17] lycoramine,[18] and haemanthidine[19]).

Acknowledgment

Financial support by the Consiglio Nazionale delle Ricerche, Roma, is much appreciated.

References

(1) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949.
(2) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.
(3) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.
(4) (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
(b) Molander, G. A.; Harris, C. H. *Chem. Rev.* **1996**, *96*, 307.



Scheme 6

Downloaded by: Simon Fraser University Library. Copyrighted material.

(5) (a) Greatrex, B. W.; Taylor, D. K.; Tiekink, E. R. T. *Org. Lett.* **2002**, *4*, 221. (b) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900. (c) For reviews see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, **1991**. (d) See also: Wovkulich, P. M. *Comprehensive Organic Synthesis*, Vol. 1; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, Chap. 3.3.

(6) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem*. **1988**, *352*, 1.

(7) **Typical Rearrangement Procedure:** Bromolactam **1** (66.0 mg, 0.25 mmol) was dissolved in the solvent (1 mL) under N_2 and the solution cooled to –45 °C. *t*-BuLi (0.29 mL of a 1.7 M solution in pentane, 0.5 mmol) was then added drop wise and the resulting clear orange solution stirred at the above temperature for 2 h. After this period, the electrophile was added and the reaction allowed warming to r.t. (about 30 min). The organic layer was washed twice with NaCl sat. solution, the water phase extracted with Et_2O and the combined organic layers dried over Na_2SO_4.
1,4-Dimethyl-3,4-dihydro-2-quinolinone (4):[20] The crude mixture was purified by flash chromatography (EtOAc–petroleum ether, 1:1) affording 104 mg (62%) of a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–6.97 (m, 4 H), 3.37 (s, 3 H), 3.05 (m, 1 H), 2.73 (dd, 1 H, *J* = 15.8, 5.6 Hz), 2.44 (dd, 1 H, *J* = 15.8, 7.6 Hz), 1.27 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 169.8, 139.8, 131.0, 127.3, 126.15, 123.0, 114.7, 39.1, 30.3, 29.4, 19.2. MS: *m/z* (%) = 175 (63), 160 (80), 132 (100), 117 (35), 91 (20), 77 (18).

(8) Krief, A.; Barbeaux, P. *Synlett* **1990**, 511.

(9) Kulkarni, V.; Cohen, T. *Tetrahedron* **1997**, *53*, 12089.

(10) **1,4-Dimethyl-3-**d**-3,4-dihydro-2-quinolinone (11a):** The crude mixture was purified by flash chromatography (Et_2O:petroleum ether, 2:3) affording 28 mg (58%) of compound **11a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–6.99 (m, 4 H), 3.37 (s, 3 H), 3.09–3.00 (m, 1 H), 2.43 (dq, 1 H, *J* = 7.2, 3.9 Hz), 1.19 (d, 3 H, *J* = 7.2 Hz). MS: *m/z* (%) = 176 (60), 161 (85), 133 (100), 91 (25), 77 (20).
1,3,4-Trimethyl-3,4-dihydro-2-quinolinone (11b):[21] The crude mixture was purified by flash chromatography (EtOAc–petroleum ether, 1:3) affording 46 mg (70%) of compound **11b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–6.82 (m, 4 H), 3.36 (s, 3 H), 2.71 (dq, 1 H, *J* = 7.4, 4.0 Hz), 2.54 (dq, 1 H, *J* = 7.2, 4.0 Hz), 1.22 (d, 3 H, *J* = 7.0 Hz), 1.11 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.9, 138.7, 129.8, 127.8, 127.3, 123.1, 114.5, 42.8, 37.8, 29.5, 20.0, 16.0. MS: *m/z* (%) = 189 (59), 174 (77), 160 (80), 146 (100), 130 (60), 117 (48), 91 (36), 77 (50).
1,4-Dimethyl-3(1-propen-2yl)-3,4-dihydro-2-quinolinone (11c): The crude mixture was purified by flash chromatography (Et_2O–petroleum ether, 2:3) affording 36 mg (67%) of compound **11c**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–6.99 (m, 4 H), 5.80–5.64 (m, 1 H), 5.00 (bd, 1 H, *J* = 10.2 Hz), 4.92 (bd, 1 H, *J* = 16.8 Hz), 3.37 (s, 3 H), 2.91–2.81 (m, 1 H), 2.60–2.53 (m, 1 H), 2.30–2.18 (m, 1 H), 2.09–1.96 (m, 1 H), 1.18 (d, 3 H, *J* = 7.4 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.6, 138.6, 135.1, 129.2, 128.0, 127.6, 123.2, 117.3, 114.6, 48.1, 34.9, 34.5, 29.4, 20.6. MS: *m/z* (%) = 215 (65), 200 (68), 173 (82), 159 (53), 130 (73), 117 (37), 91 (41), 77 (50), 41 (100).
1,4-Dimethyl-(1-phenylmethanol)-3,4-dihydro-2-quinolinone (11d): The crude mixture was purified by flash chromatography (EtOAc–petroleum ether, 1:1) affording 54 mg (60%) of compound **11d**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.18 (m, 5 H), 7.16–7.03 (m, 4 H), 4.38 (dd, 1 H, *J* = 10.2 Hz, *J* = 2.6 Hz), 3.46 (s, 3 H), 2.95 (d, 1 H, *J* = 2.6 Hz), 2.77 (dd, 1 H, *J* = 10.2 Hz, *J* = 1.4 Hz), 2.46–2.42 (m, 1 H), 1.08 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.4, 141.9, 138.3, 128.9, 128.6, 128.5, 128.3, 128.0, 127.7, 126.6, 123.6, 115.0, 73.3, 56.6, 33.4, 29.7, 21.2. MS: *m/z* (%) = 281 (1.5), 175 (5), 160 (100), 146 (4), 132 (6), 117 (6), 91 (7), 77 (17).

(11) (a) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435. (b) Kessar, S. V.; Singh, P.; Chawla, R.; Kumar, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1074.

(12) **2,5-Dimethyl-1,2,4,5-tetrahydro-benzo[*c*]azepin-3-one (20):** The crude mixture was purified by flash chromatography (EtOAc–petroleum ether, 10:1) affording 72 mg (60%) of compound **20**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.05 (m, 4 H), 4.47 (AB system, 2 H), 3.39–3.25 (m, 1 H), 3.11 (m, 1 H), 3.05 (s, 3H), 2.72 (m, 1 H), 1.37 (d, 3 H, *J* = 7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.4, 142.8, 133.6, 130.3, 130.2, 128.6, 128.1, 125.8, 54.6, 41.0, 33.5, 29.7, 24.5. MS: *m/z* (%) = 243 (2.5), 189 (100), 174 (87), 159 (74), 129 (100).

(13) **2,5,5-Trimethyl-1,2,4,5-tetrahydro-benzo[*c*]azepin-3-one (23a):** The crude mixture was purified by flash column chromatography (CH_2Cl_2–MeOH, 98:2) affording 72 mg (74%) of compound **23a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 1 H), 7.33–7.24 (m, 1 H), 7.15–6.99 (m, 2 H), 4.47 (s, 2 H), 3.03 (s, 3 H), 2.87 (s, 2 H), 1.40 (s, 6 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.5, 146.6, 133.3, 129.6, 129.5, 128.6, 126.1, 55.9, 48.4, 34.8, 33.3, 28.5, 28.4. MS: *m/z* (%) = 203 (44), 188 (14), 174 (8), 145 (87).
2,5-Dimethyl-5(prop-3-enyl)-1,2,4,5-tetrahydro-benzo[*c*]azepin-3-one (23b): The crude mixture was purified by flash chromatography (CH_2Cl_2–MeOH, 98:2) affording 54 mg (50%) of compound **23b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 2 H), 7.16–7.00 (m, 2 H), 5.62–5.44 (m, 1 H), 5.02 (bd, 1 H, *J* = 17.2 Hz), 5.00 (bd, 1 H, *J* = 10.6 Hz), 4.86 (d, 1 H, *J* = 16.2 Hz), 3.98 (d, 1 H, *J* = 16.2 Hz), 3.34 (d, 1 H, *J* = 13.6 Hz), 3.01 (s, 3 H), 2.68 (ddt, 1 H, *J* = 14.0, 5.8, 1.4 Hz), 2.37 (d, 1 H, *J* = 13.6 Hz), 2.26 (dd, 1 H, *J* = 14.0, 8.8 Hz), 1.40 (s, 3 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.6, 144.9, 138.1, 134.4, 134.3, 129.5, 128.7, 126.1, 118.6, 55.8, 50.2, 45.2, 40.0, 34.6, 31.5. MS: *m/z* (%) = 229 (1), 201 (3), 188 (7), 146 (100).
2,5-Dimethyl-5(hydroxyphenylmethyl)-1,2,4,5-tetrahydro-benzo[*c*]azepin-3-one (23c): The crude mixture was purified by flash chromatography (CH_2Cl_2–MeOH, 98:2) affording 88 mg (64%) of compound **23c**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.47 (dd, 1 H, *J* = 8.0, 1.2 Hz), 7.36–7.24 (m, 6 H), 7.21–7.05 (m, 2 H), 4.91 (d, 1 H, *J* = 16.2 Hz), 4.90 (bs, 1 H), 3.96 (d, 1 H, *J* = 16.2 Hz), 3.59 (d, 1 H, *J* = 13.6 Hz), 2.98 (s, 3 H), 2.37 (bs, 1 H), 2.22 (d, 1 H, *J* = 13.6 Hz), 1.34 (d, 3 H, *J* = 7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.8, 143.2, 139.7, 135.9, 130.0, 129.9, 129.7, 128.8, 128.5, 128.1, 128.0, 126.7, 126.6 83.0, 56.0, 45.8, 40.9, 34.5, 27.8. MS: *m/z* (%) = 189 (80), 174 (100), 160 (17), 146 (48), 115 (41).

(14) Desos, P.; Schlewer, G.; Lugnier, C.; Beretz, A.; Maffrand, J. P.; Bernat, A.; Wermuth, C. G. *Eur. J. Med. Chem.* **1991**, *26*, 189.

(15) Olesen, H.; Cowan, D.; Bruunshuus, I.; Klempel, K.; Hill, G. *Pure Appl. Chem.* **1997**, *69*, 1081.

(16) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.

(17) Chaplin, D. A.; Johnson, N. B.; Paul, J. M.; Potter, G. A. *Tetrahedron Lett.* **1998**, *39*, 6777.

(18) Lee, T. B. K.; Goehring, K. E.; Ma, Z. *J. Org. Chem.* **1998**, *63*, 4535.

(19) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586.

(20) Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 353.

(21) Clark, A. J.; Jones, K. *Tetrahedron* **1992**, *33*, 6875.

Downloaded by: Simon Fraser University Library. Copyrighted material.