Tetrahedron Letters 51 (2010) 1790–1792

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of bridged 1,4-diazepane derivatives via Schmidt reactions

Andrey P. Mityuk [a], Aleksandr V. Denisenko [a], Oleksandr P. Dacenko [a], Oleksandr O. Grygorenko [a,b,*], Pavel K. Mykhailiuk [a,b,*], Dmitriy M. Volochnyuk [a], Andrey A. Tolmachev [a,b]

[a] Enamine Ltd, Alexandra Matrosova Street 23, Kyiv 01103, Ukraine
[b] Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska Street 64, Kyiv 01033, Ukraine

ARTICLE INFO

Article history:
Received 2 December 2009
Revised 12 January 2010
Accepted 29 January 2010
Available online 4 February 2010

ABSTRACT

A series of bridged 1,4-diazepanes (i.e., diazabicyclo[*n*.3.2]alkanes, *n* = 3–5) selectively protected at one of the nitrogen atoms was prepared, for possible application in drug design, via Schmidt rearrangement of the corresponding ketones.

Though combinatorial chemistry remains an essential part of drug discovery, so far this approach has demonstrated a poor success rate, presumably due to the rather limited chemical space covered by the products obtained. This is partially due to classical combinatorial libraries suffering from lack of molecular rigidity.[1] Fragment-based drug design which became a novel paradigm for drug discovery in the last decade[2] also appeared to require conformationally restricted and rigid building blocks. Due to a predefined spatial orientation of the molecular fragments located on a conformationally rigid scaffold, a decrease in entropy of binding of the molecule with its biological target might be expected, thus leading to higher affinity of the potential drug candidate.[3]

Aliphatic diamines exemplify privileged structures among other small molecules of importance to drug discovery.[4] Conformationally restricted diamines have been widely used in drug design; in particular, piperazine **1** and 1,4-diazepane **2** scaffolds are constituents of Sildenafil **3**[5] and Fasudil **4**,[6] and compounds with antibacterial **5**,[7] nootropic and antiamyloidogenic **6**[8] activities (Fig. 1).

In this Letter, we report our results on the synthesis of bridged 1,4-diazepanes **7**–**10** (Scheme 1). Retrosynthetic analysis of **7**–**10** leads to *N*-benzyl azabicyclo[*n*.3.1]alkanones **11**–**14** as convenient starting materials which are readily prepared by double Mannich annelation of the corresponding cycloalkanones.[9] It should be noted that the synthetic approach should consider the possibility of generating diamines **7**–**10** monoprotected at one of the nitrogen atoms; this feature is essential for further selective modification.

To achieve ring expansion of the bicyclic cores of **11**–**14**, we decided to use classical Schmidt reaction conditions (sodium azide–sulfuric acid).[10] It emerged that the bridge length in molecules of **11**–**14** is a crucial factor that determines the reaction outcome. In particular, in the case of azabicyclo[3.2.1]octane derivative **11**, fragmentation occurred instead of rearrangement leading to the formation of tetrahydro-1*H*-azepine **15** in 71% yield.[11] When ketone **12** was submitted to the Schmidt reaction, a mixture of hexahydroazocine **16**[12] (23%) and diazabicyclo[3.3.2]decane **17**[13] (40%) was obtained. Finally, rearrangement

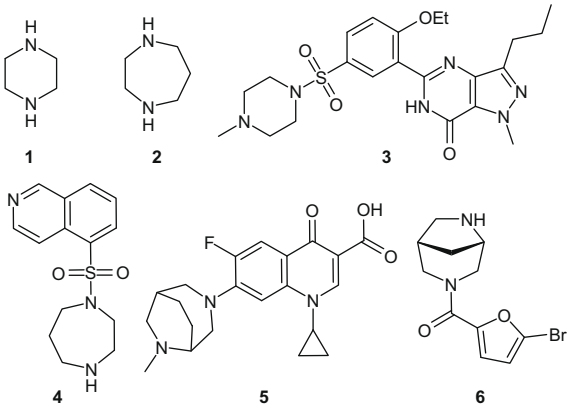
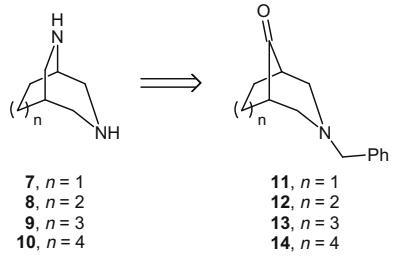


Figure 1.



7, *n* = 1
8, *n* = 2
9, *n* = 3
10, *n* = 4

11, *n* = 1
12, *n* = 2
13, *n* = 3
14, *n* = 4

Scheme 1.

* Corresponding authors. Tel.: +38 044 239 33 15; fax: +38 044 502 48 32.
E-mail addresses: gregor@univ.kiev.ua (O.O. Grygorenko), pashamk@gmx.de (P.K. Mykhailiuk).

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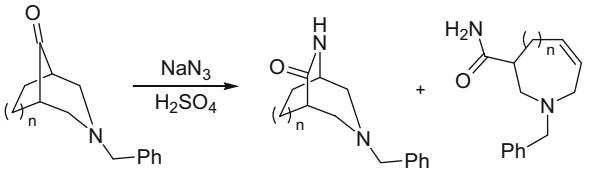
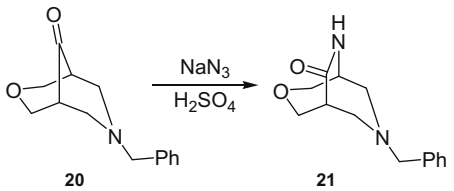
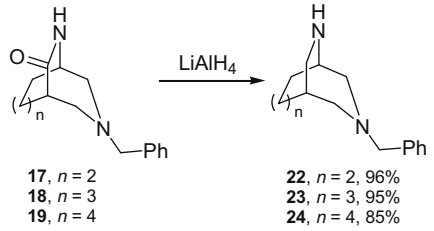
doi:10.1016/j.tetlet.2010.01.121



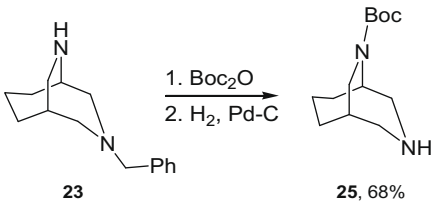
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

of compounds **13** and **14** resulted in exclusive formation of amides **18**[14] (65%) and **19**[15] (60%), respectively (Scheme 2). This effect appears to be very sensitive to modification of the bicyclic core, in particular, compound **20** gives only the usual bicyclic Schmidt rearrangement product **21** under these reaction conditions (Scheme 3).[16]

Compounds **17**–**19** were reduced with lithium aluminium hydride to afford monoprotected diamine derivatives **22**–**24** suitable for further selective modification (Scheme 4).[17–19]

An ability to obtain orthogonally monoprotected diazabicycloalkane derivatives (i.e., **25**) was also demonstrated in the case of the diamine **8** (Scheme 5).[20]

In conclusion, an expedient approach to selectively monoprotected derivatives of diamines **8**–**10** (compounds **22**–**25**) which are of interest for drug design has been developed.

Acknowledgement

The authors are thankful to Olga V. Manoylenko for her invaluable help with chromatographic separations.

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11. *Schmidt reaction of ketones* **11**–**14** *(general procedure, the reaction of 3-benzyl-3-aza-bicyclo[3.2.1]octan-8-one (***11***) is given as an example):* To a mixture of $CHCl_3$ (66 mL) and H_2SO_4 (40 g), ketone **11** (9.4 g, 44 mmol) was added slowly followed by NaN_3 (3.4 g) at 10–20 °C with stirring (*Caution*: External cooling should be used). The resulting mixture was stirred overnight, then slowly added to an excess of saturated aqueous $NaHCO_3$ (700 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and then evaporated to dryness. The residue was recrystallized from benzene–hexanes to give 7.1 g (31 mmol, 71%) of 1-benzyl-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxamide (**15**) as a white solid. Mp 109 °C. MS (*m*/*z*, CI): 231 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.37; H, 8.03; N, 11.96. ^{1}H NMR ($CDCl_3$), δ: 7.61 (br s, 1H, CONH*H*), 7.35 (t, *J* = 7.0 Hz, 2H, C_6H_5), 7.30 (m, 3H, C_6H_5), 5.88 (m, 1H, 5- or 6-C*H*), 5.77 (m, 1H, 5- or 6-C*H*), 5.75 (br s, 1H, CONH*H*), 3.66 (d, *J* = 13.1 Hz, 1H, C*H*HC$_6$H$_5$), 3.62 (d, *J* = 13.1 Hz, 1H, CH*H*C$_6$H$_5$), 3.28 (m, 2H), 3.01 (dd, *J* = 15.2 and 4.4 Hz, 1H), 2.80 (dd, *J* = 13.0 and 2.2 Hz, 1H, C*H*H), 2.69 (m, 1H), 2.63 (m, 1H), 2.46 (d, *J* = 15.2 Hz, 1H). ^{13}C NMR ($CDCl_3$), δ: 177.1 (*C*=O), 138.1 (1-C of C_6H_5), 131.2 (*C*H), 129.5 (*C*H), 129.0 (*C*H), 128.5 (*C*H), 127.5 (*C*H), 63.1 (CH_2), 60.6 (CH_2), 54.3 (CH_2), 43.4 (3-*C*H), 30.7 (4-CH_2).
12. 1-Benzyl-1,2,3,4,5,8-hexahydro-azocine-3-carboxamide (**16**) was obtained from 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one (**12**) in 23% (1.8 g) yield after purification by flash chromatography of the mother liquor obtained by recrystallization of **17** [hexanes–2-propanol (3:1)]. Mp 88–89 °C (benzene–hexanes). MS (*m*/*z*, CI): 245 (MH^+). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.99; H, 8.51; N, 11.09. ^{1}H NMR ($CDCl_3$), δ: 7.33 (m, 4H, C_6H_5), 7.29 (m, 1H, 4-CH of C_6H_5), 6.69 (br s, 1H, N*H*), 5.89 (m, 1H, C*H*=CH), 5.60 (br s, 1H, NH*H*), 5.56 (m, 1H, CH=C*H*), 3.67 (d, *J* = 13.2 Hz, 1H, C*H*HC$_6$H$_5$), 3.61 (d, *J* = 13.2 Hz, 1H, CH*H*C$_6$H$_5$), 3.41 (dd, *J* = 15.4 and 6.5 Hz, 1H, 8-C*H*H), 3.11 (dd, *J* = 15.4 and 6.3 Hz, 1H, 8-C*H*H), 3.00 (dd, *J* = 13.2 and 7.8 Hz, 1H, 2-C*H*H), 2.82 (d, *J* = 13.2 Hz, 1H, 2-CH*H*), 2.79 (m, 1H), 2.66 (m, 1H), 2.27 (m, 1H), 1.99 (m, 1H), 1.88 (m, 1H). ^{13}C NMR ($CDCl_3$), δ: 178.1 (*C*=O), 138.8, 132.6, 129.1, 128.6, 127.4, 125.5, 61.6 ($CH_2C_6H_5$), 55.5, 50.6, 43.3, 30.2, 25.3.
13. 3-Benzyl-3,9-diaza-bicyclo[3.3.2]decan-10-one (**17**) was obtained from 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one (**12**) in 40% (3.1 g) yield. Mp 158 °C (benzene). MS (*m*/*z*, CI): 245 (MH^+). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.52; H, 8.09; N, 11.70. ^{1}H NMR ($CDCl_3$), δ: 7.35 (m, 4H, C_6H_5), 7.27 (m, 1H, 4-C*H* of C_6H_5), 7.21 (br d, *J* = 6.2 Hz, 1H, N*H*), 3.57 (d, *J* = 13.1 Hz, 1H, C*H*HC$_6$H$_5$), 3.51 (d, *J* = 13.1 Hz, 1H, CH*H*C$_6$H$_5$), 3.39 (q, *J* = 6.6 Hz, 1H, 1-C*H*), 2.84 (dd, *J* = 12.4 and 5.0 Hz, 1H), 2.76 (m, 2H), 2.45 (d, *J* = 11.7 Hz, 1H), 2.37 (d, *J* = 13.1 Hz, 1H), 2.11 (m, 1H), 1.76–1.97 (m, 4H), 1.52 (m, 1H). ^{13}C NMR ($CDCl_3$), δ: 179.4 (*C*=O), 138.9 (1-C_6H_5), 129.0 (*C*H), 128.4 (*C*H), 127.2 (*C*H), 63.6 (CH_2), 61.5 (CH_2), 55.6 (CH_2), 48.5 (*C*H), 45.7 (*C*H), 27.9 (CH_2), 23.8 (*C*H), 22.8 (*C*H).
14. 8-Benzyl-8,10-diaza-bicyclo[4.3.2]undecan-11-one (**18**) was obtained from 8-benzyl-8-azabicyclo[4.3.1]decan-10-one (**13**) in 65% (6.2 g) yield. Mp 126 °C (benzene). MS (*m*/*z*, CI): 259 (MH^+). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.02; H, 8.85; N, 11.07. ^{1}H NMR (DMSO-d_6), δ: 7.51 (br d, *J* = 6.8 Hz, 1H, N*H*), 7.35 (m, 4H, C_6H_5), 7.27 (m, 1H, 4-C*H* of C_6H_5), 3.49 (m, 2H, $CH_2C_6H_5$), 3.28 (m, 1H), 2.92 (d, *J* = 11.9 Hz, 1H), 2.64 (d, *J* = 11.9 Hz, 1H), 2.51 (m, 1H), 2.25 (d, *J* = 11.9 Hz, 2H), 2.09 (m, 2H), 1.92 (m, 1H), 1.73 (m, 1H), 1.61 (m, 2H), 1.43 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 180.6 (*C*=O), 138.8 (1-C of C_6H_5), 129.4 (*C*H), 128.5 (*C*H), 127.4 (*C*H), 64.9 (CH_2), 62.5 (CH_2), 57.7 (CH_2), 51.5 (*C*H), 47.2 (*C*H), 36.6 (CH_2), 33.4 (CH_2), 26.1 (CH_2), 24.9 (CH_2).
15. 9-Benzyl-9,11-diaza-bicyclo[5.3.2]dodecan-12-one **19** was obtained from 9-benzyl-9-azabicyclo[5.3.1]undecan-11-one **14** in 60% (5.8 g) yield. Mp 180 °C (benzene). MS (*m*/*z*, CI): 273 (MH^+). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.37; H, 9.13; N, 10.01. ^{1}H NMR ($CDCl_3$), δ: 7.34 (m, 4H, C_6H_5), 7.26 (m, 1H, 4-C*H* of C_6H_5), 6.39 (br s, 1H, N*H*), 3.63 (d, *J* = 13.1 Hz, 1H, C*H*HC$_6$H$_5$), 3.57 (d, *J* = 13.1 Hz, 1H, C*H*HC$_6$H$_5$), 3.20 (m, 1H), 2.80 (m, 2H), 2.66 (m, 1H), 2.45 (m, 2H), 2.34 (m, 1H), 1.91 (m, 1H), 1.68–1.85 (m, 5H), 1.36 (m, 3H). ^{13}C NMR ($CDCl_3$), δ: 179.3 (*C*=O), 139.2 (1-C of C_6H_5), 129.1 (*C*H), 128.5

(CH), 127.3 (CH), 64.2 (CH_2), 60.4 (CH_2), 55.4 (CH_2), 50.6 (CH), 47.8 (CH), 31.7 (CH_2), 29.4 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 23.5 (CH_2).

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17. Reduction of amides **17**–**19** (general procedure, synthesis of 3-benzyl-3,9-diaza-bicyclo[3.3.2]decane (**22**) is given as an example): to a suspension of $LiAlH_4$ (4.7 g) in dry THF (200 mL), a solution of amide **17** (10 g, 41 mmol) in THF (100 mL) was added dropwise, and the resulting mixture was refluxed for 36 h with stirring. Then H_2O (20 mL) was added carefully, and the mixture was stirred for 15 min. The precipitate was filtered off and washed with THF (5 × 100 mL). The filtrate was evaporated and distilled (127 °C/0.5 mmHg) to give 9.0 g (39 mmol, 96%) of diamine **22**. MS (*m*/*z*): 231 (MH^+). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.02; H, 9.27; N, 12.38. ^1H NMR ($CDCl_3$), δ: 7.28 (m, 4H, C_6H_5), 7.18 (m, 1H, 4-C*H* of C_6H_5), 3.48 (d, *J* = 13.3 Hz, 1H, C*H*HC_6H_5), 3.42 (d, *J* = 13.3 Hz, 1H, CH*H*C_6H_5), 3.25 (m, 1H, 1-C*H*), 3.02 (m, 2H), 2.93 (m, 2H), 2.53 (br s, 1H, N*H*), 2.41 (m, 1H), 2.33 (d, *J* = 12.0 Hz, 1H), 2.28 (d, *J* = 12.0 Hz, 1H), 2.01 (m, 1H, 5-C*H*), 1.93 (m, 2H), 1.60–1.70 (m, 3H). ^{13}C NMR ($CDCl_3$), δ: 139.7 (1-C_6H_5), 128.4 (CH), 127.9 (CH), 126.5 (CH), 63.6 (CH_2), 61.6 (CH_2), 61.2 (CH_2), 54.0 (1-CH), 51.5 (CH_2), 36.5 (5-CH), 32.8 (CH_2), 30.6 (CH_2), 23.2 (CH_2).
18. 8-Benzyl-8,10-diaza-bicyclo[4.3.2]undecane (**23**) was obtained from amide **18** in 95% (5.4 g) yield. Bp 139 °C/0.5 mmHg. MS (*m*/*z*): 245 (MH^+). Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.94; H, 9.63; N, 11.48. ^1H NMR ($CDCl_3$), δ: 7.33 (m, 4H, C_6H_5), 7.24 (m, 1H, 4-C*H* of C_6H_5), 3.62 (d, *J* = 12.7 Hz, 1H, C*H*HC_6H_5), 3.39 (d, *J* = 12.7 Hz, 1H, CH*H*C_6H_5), 3.35 (m, 1H), 3.16 (d, *J* = 14.2 Hz, 1H), 2.93 (dd, *J* = 14.2 and 5.2 Hz, 1H), 2.88 (ddd, *J* = 11.7, 3.2 and 1.8 Hz, 1H), 2.58 (ddd, *J* = 13.6, 5.2 and 1.8 Hz, 1H), 2.49 (d, *J* = 13.6 Hz, 1H), 2.28 (d, *J* = 11.7 Hz, 1H), 2.12 (m, 1H), 1.96 (m, 2H), 1.85 (m, 1H), 1.77 (br s, 1H, N*H*), 1.56–1.70 (m, 3H), 1.43–1.52 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 139.8 (1-C of C_6H_5), 129.6 (CH), 128.2 (CH), 127.0 (CH), 64.9 (CH_2), 62.8 (CH_2), 58.3 (1-CH), 50.1 (CH_2), 38.6 (6-CH), 33.9 (CH_2), 32.8 (CH_2), 25.4 (CH_2), 25.2 (CH_2).
19. 9-Benzyl-9,11-diaza-bicyclo[5.3.2]dodecane (**24**) was obtained from amide **19** in 85% (4.8 g) yield. Bp 151 °C/0.5 mmHg. Alternatively, purification could be performed by flash chromatography [Et_2O–MeOH (2:1) as eluent]. MS (*m*/*z*, EI): 258 (M^+), 191 (M^+–C_7H_7), 134, 91 ($C_7H_7^+$). Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 78.77; H, 10.45; N, 10.49. ^1H NMR ($CDCl_3$), δ: 7.36 (m, 4H, C_6H_5), 7.30 (m, 1H, 4-CH of C_6H_5), 3.78 (s, 1H), 3.67 (s, 1H), 3.65 (d, *J* = 13.0 Hz, 1H, C*H*HC_6H_5), 3.58 (d, *J* = 13.0 Hz, 1H, CH*H*C_6H_5), 3.20 (s, 1H), 3.00 (d, *J* = 14.3 Hz, 1H), 2.88 (dd, *J* = 14.4 and 5.1 Hz, 1H), 2.80 (m, 2H), 2.66 (d, *J* = 14.0 Hz, 1H), 1.83–2.19 (m, 5H), 1.70 (m, 3H), 1.57 (m, 1H), 1.45 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 138.8 (1-C of C_6H_5), 129.9 (CH), 128.1 (CH), 127.0 (CH), 65.2 (CH_2), 60.9 (CH_2), 59.0 (CH_2), 54.8 (1-CH), 49.8 (CH_2), 38.7 (6-CH), 35.0 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 26.1 (CH_2), 26.0 (CH_2).
20. *Procedure for the synthesis of* **25**: To a solution of amine **23** (8.6 g, 37 mmol) in Et_2O (100 mL), a solution of NaOH (6 g, 0.150 mol) in H_2O (30 mL) was added. To the resulting mixture, a solution of Boc_2O (9.8 g, 45 mmol) in Et_2O (30 mL) was added dropwise. The reaction mixture was stirred overnight, then the aqueous phase was separated and washed with Et_2O (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in MeOH (80 mL) and hydrogenated over 20% $Pd(OH)_2$ on charcoal at 50 bar and at 40 °C for 5 h. The catalyst was filtered off, and the solvent was removed in vacuo. The residue was purified by flash chromatography [hexane–2-propanol (gradient 9:1 to 1:1) as eluent] to give *tert*-butyl 3,9-diazabicyclo[3.3.2]decane-9-carboxylate (**25**) (6.1 g, 25 mmol, 68%). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66. Found: C, 65.19; H, 10.25; N, 11.31. MS (*m*/*z*, EI): 240 (M^+), 184 (M^+–$(CH_3)_2C{=}CH_2$), 167 (M^+–$(CH_3)_3CO$), 139, 110, 96, 82, 68, 57. The product was obtained as a mixture of *E*/*Z* rotamers at the amide bond. ^1H NMR ($CDCl_3$): 4.71 (s, 0.6H, 1-C*H*), 4.48 (s, 0.4H, 1-C*H*), 3.77 (d, *J* = 12.8 Hz, 0.4H, 10-CH*H*), 3.66 (d, *J* = 12.8 Hz, 0.6H, 10-CH*H*), 3.43 (d, *J* = 12.8 Hz, 0.6H, 10-CH*H*), 3.41 (d, *J* = 12.8 Hz, 0.4H, 10-CH*H*), 3.06 (m, 2H), 2.79 (m, 2H), 2.16 (s, 0.4H, 5-C*H*), 2.11 (s, 0.6H, 5-C*H*), 1.94 (m, 1H), 1.85 (m, 2H), 2.57 (m, 2H), 1.55 (m, 1H), 1.47 (m, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): 155.7 and 155.4 (C=O), 79.2 ($(CH_3)_3C$), 54.9, 54.8, 54.7, 53.8, 53.4, 52.8, 51.9, 51.4, 34.9, 34.7, 29.1, 29.0, 28.7 and 28.6 ($(CH_3)_3C$), 28.2, 27.9, 22.7 and 22.6.