Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5727–5730

TETRAHEDRON LETTERS

# Synthesis of alkylated iridolactone analogs

Zineb Guerrab,[a,b] Boujemaâ Daou,[a] Souad Fkih-Tetouani,[a] Mohammed Ahmar[b] and Bernard Cazes[b,*]

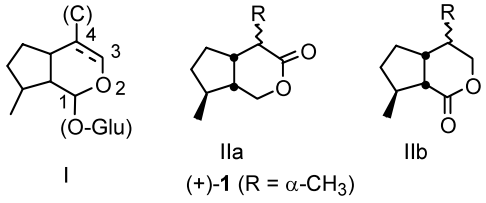
[a]*Université Mohammed V-Agdal, Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Av. Ibn Battouta, BP 1014 Rabat, Morocco*

[b]*Université Claude Bernard-Lyon, Laboratoire de Chimie Organique I, associé au CNRS, Bât. CPE-Lyon, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France*

Received 22 May 2003; accepted 26 May 2003

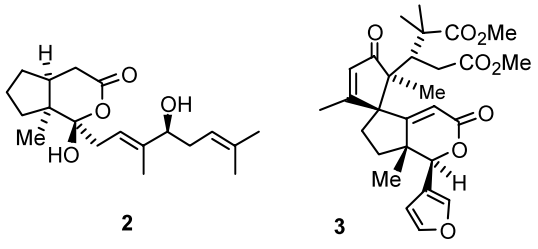
**Abstract**—Bicyclic δ-lactones, iridolactones analogs with an alkyl group at the bicyclic junction, are obtained from α-alkyl-α-hydroxymethylcyclopentanones via an intramolecular Horner–Wadsworth–Emmons reaction.


Iridoids are important monoterpene natural products which are characterized by a functionalized *cis*-fused cyclopenta[*c*]pyran skeleton I.[1] A large part of these compounds present a β-non reducing link to a sugar unit at C1 and a double bond at C3–C4 (Scheme 1). A sub-class of non-glycosidic iridoids, referred to as iridoid lactones II, is composed of cyclopentanoid compounds fused to a δ-lactone unit.[2] These bicyclic lactones are further divided in two sub-groups IIa,b according to the position of the lactone keto group. Particularly, iridomyrmecin (+)-**1**—the first isolated and identified iridoid compound isolated from *Iridomyrmex humilis* ants—belongs to sub-group IIa.[3]



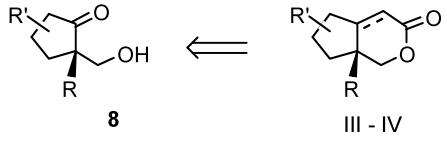

**Scheme 1.**

Iridoids have significant biological activities ranging from sedative to antimicrobial or antileukemic effects.[4] To the best of our knowledge, naturally occuring compounds with a substituent at the bicyclic junction of an 3-oxa-bicyclo[4.3.0]nonane core are scarce. Diterpenes xestolide **2** and guyanin **3** present such bicyclic structures (Scheme 2).[5,6]




**Scheme 2.**

We recently undertook a project aimed at synthesizing new unsaturated III and saturated analogs IV of iridolactone IIa with an alkyl group at the bicyclic junction, and report herein our approach from α-alkyl-α-hydroxymethylcyclopentanones **8** using an intramolecular Horner–Wadsworth–Emmons reaction (Scheme 3).[7]

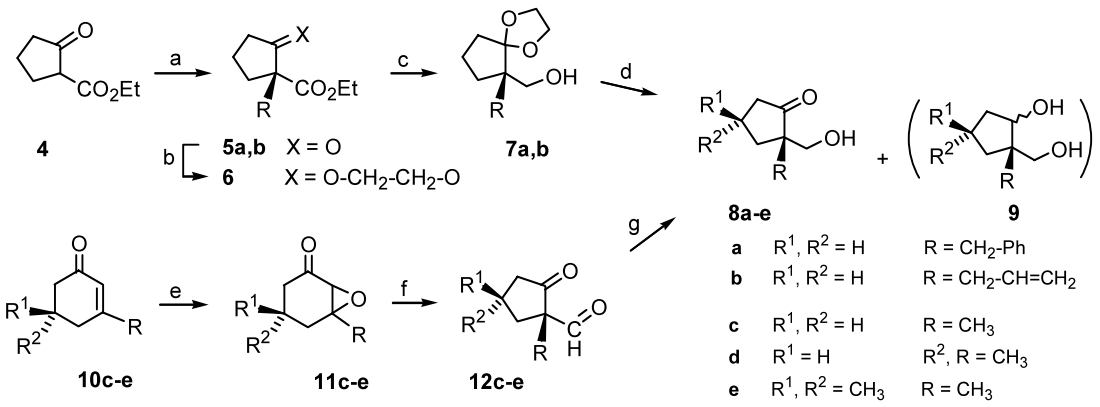



**Scheme 3.**

The precursor β-ketoalcohols **8a**,**b** and **8c**–**e** were, respectively, prepared according to two sequences depicted in Scheme 4. The first one made use of the reduction of the ethyleneketals **6** of β-ketoesters **5**.[8]

* Corresponding author. Fax: +33.4.72.43.12.14; e-mail: cazes@univ-lyon1.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01320-0



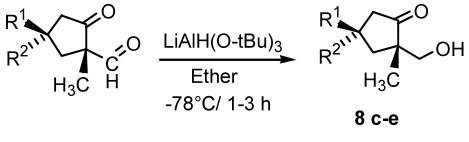

**Scheme 4.** *Reagents and conditions*: (a) $K_2CO_3$, R-Br, acetone, rt, 24 h (88–93%); (b) glycol, cat. *p*-TsOH, toluene/Dean–Stark (90%); (c) $AlLiH_4$, ether, 0°C, 1 h; (d) cat. 6N HCl, THF, rt, 6 h (88–93%); (e) $H_2O_2$/NaOH, EtOH, 0–20°C (79–85%); (f) $BF_3$–$Et_2O$ (0.75 equiv.), $CH_2Cl_2$, 0°C (50–77%); (g) $LiAlH(O\text{-}tBu)_3$ (1 equiv.) [$AlLiH_4$, 3 equiv. *t*-BuOH, $Et_2O$, −40°C, 4 h], $Et_2O$, −78°C, 1–3 h (52–78%).

This standard procedure was preferred to the more direct selective reduction of β-ketoesters **5** via enolate protection,[9] which in our hands also gave some diols **9**.

The second sequence involved the well documented Lewis acid-mediated rearrangement of epoxycyclohexenones **11** to β-ketoaldehydes **12**,[10] followed by the chemoselective reduction of the formyl group by lithium tri-*ter*-butoxyaluminum hydride[11] according to Welzel et al.[10c,12] This second route was realized from commercially available substituted 3-methylcyclohexenones such as isophorone **10e**. It advantageously allowed the synthesis of polysubstituted β-ketoalcohols **8**. It is worth noting that β-ketoaldehyde **12d** was obtained as a 80:20 mixture of *trans–cis* diastereomers as already described.[10d] Consequently, its reduction gave the β-ketoalcohol **8d** with the same diastereomeric 80:20 ratio (Schemes 4–6 show only the major *trans* diastereomer with the two methyl groups in *trans* position).

However this chemoselective reduction was critical, and it turned out that its success was largely dependent on the preparation step of the hindered $LiAlH(O\text{-}tBu)_3$ from *t*-butanol and a titrated ethereal $LiAlH_4$ solution. The best results were obtained with a reducing agent generated in situ at −40°C during 4 h, which gave a 57–100% conversion and suppressed the overreduction to diol **9**. The reduction of β-ketoaldehydes **12c–e** at −78°C for 1–3 h then afforded chemoselectively α-hydroxymethylcyclopentanones **8c–e** in 52–78% yield (Scheme 5).

The synthesis of δ-lactones **14** and **15** from the β-ketoalcohols **8** is summarized in Scheme 6 and Table 1 (entries 1–5). The transformation of these precursor β-ketoalcohols **8** to diethylphosphonoacetates **13** was




| | | | |
|---|---|---|---|
| **12 c** | $R^1$, $R^2$ = H | 52% | (57%) |
| **d** | $R^1$ = H $R^2$ = $CH_3$ (80:20 *trans-cis*) | 59% | (63%) |
| **e** | $R^1$, $R^2$ = $CH_3$ | 78% | (100%) |

(conversion)

**Scheme 5.**

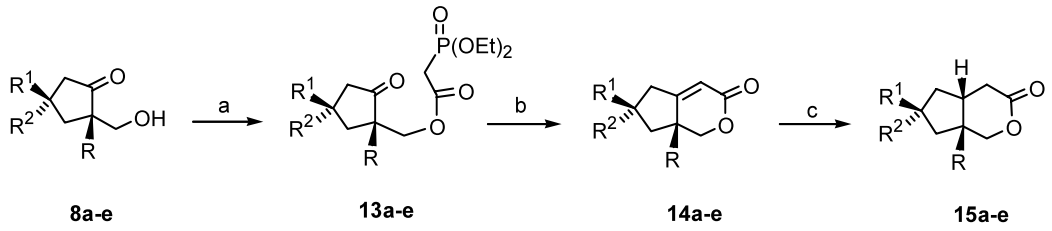
easily realized by their DMAP-catalyzed esterification in the presence of dicyclohexylcarbodiimide DCC.[13]

The intramolecular Horner–Wadsworth–Emmons reaction then occurred by treatment of phosphonoacetates **13a–e** with $LiBr$–$NEt_3$ according to a procedure used for base sensitive materials.[14] Unsaturated lactones **14a–e** were obtained with satisfactory 70–80% yield.[15] Finally, the hydrogenation of these lactones **14** to *cis* δ-lactones **15** was classically carried out in ethyl acetate under palladium/charcoal-catalyzed conditions (96–98% yield).

In conclusion, we have shown that iridoid-like bicyclic δ-lactones **14** and **15** with an alkyl group at the bicyclic junction are easily obtained by the intramolecular Horner–Wadsworth–Emmons reaction of the intermediate diethylphosphonoacetates of α-alkyl-α-hydroxymethylcyclopentanones.

## Acknowledgements

One of us (Z.G.) thanks *Région Rhône-Alpes* for a doctoral fellowship (MIRA program).




**Scheme 6.** *Reagents and conditions*: (a) $(EtO)_2PO\text{-}CH_2\text{-}CO_2H$ (1 equiv.), DCC (1 equiv.), 6 mol% DMAP, $CH_2Cl_2$, rt, 3 h; (b) LiBr (3.2 equiv.), $NEt_3$ (10 equiv.), THF, rt, 3–4 h; (c) $H_2$, cat Pd/C, AcOEt, rt, 20 h.

**Table 1.** Synthesis of bicyclic δ-lactones **14–15**

| Entry | β-Ketoalcohols **8a–e** | $R^1$, $R^2$ | R | Yields (%)[a] | | |
|---|---|---|---|---|---|---|
| | | | | **13a–e** | **14a–e** | **15a,c–e** |
| 1 | **8a** | $R^1=R^2=H$ | $R=CH_2\text{-}Ph$ | 91 | 80 | 96 |
| 2 | **8b** | $R^1=R^2=H$ | $R=CH_2\text{-}CH{=}CH_2$ | 80 | 85 | – (94)[d] |
| 3 | **8c** | $R^1=R^2=H$ | $R=CH_3$ | 82 | 70 | 97 |
| 4 | **8d**[b] | $R^1=H$, $R^2=CH_3$ | $R=CH_3$ | 90[c] | 71[c] | 98[c] |
| 5 | **8e** | $R^1=R^2=CH_3$ | $R=CH_3$ | 90 | 70 | 98 |

[a] Refers to yield of isolated product by flash-chromatography.
[b] β-Ketoalcohol **8d** was a *trans–cis* 80:20 mixture of diastereomers (major *trans*-diastereomer shown in Scheme 6).
[c] Lactones **14d** and **15d** obtained as 80:20 mixtures of diastereomers.
[d] Hydrogenation gave the fully saturated lactone with 94% yield.

## References


1. For reviews, see: (a) Bobitt, J. M.; Segebarth, K. P. *Cyclopentanoid Terpene Derivatives*; Marcel Dekker: New York, 1969; (b) Bianco, A. In *Studies in Natural Products Chemistry*; Rhaman, A. U., Ed.; Elsevier: Amsterdam, 1990; Vol. 7, p. 439; (c) Franzyk, H. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Falk, H.; Kirby, G. W.; Moore, R. E., Eds.; Springer-Verlag: Wien, 2000; Vol. 73, pp. 1–114.
2. Nangia, A. *Tetrahedron* **1997**, *53*, 14507–14545.
3. (a) Pavan, M. *Ric. Sci.* **1949**, *19*, 1011; (b) Pavan, M. *Chim. e Industr.* **1955**, *37*, 625; (c) Fusco, R.; Trave, R.; Vercellone, A. *Chim. e Industr.* **1955**, *37*, 958; (d) Bates, B. B.; Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1958**, *80*, 3420–3424; (e) McConnell, J. F.; Mathieson, A. McL.; Schoenborn, B. P. *Tetrahedron Lett.* **1962**, *2*, 445–448.
4. Ghisalberti, E. L. *Phytomedicine* **1998**, *5*, 147–163.
5. Northcote, P. T.; Andersen, R. J. *Can. J. Chem.* **1988**, *67*, 1359–1362.
6. McLean, S.; Perpick-Dumont, M.; Reynolds, W. F.; Sawyer, J. F.; Jacob, H.; Ramdayal, F. *J. Am. Chem. Soc.* **1988**, *110*, 5339–5344.
7. For uses of the intramolecular HWE reaction for the synthesis of γ- and δ-lactones, see: (a) Mickolajczyk, M.; Midura, W. H. *Synlett* **1991**, 245–247; (b) Nangia, A.; Rao, P. B. *Tetrahedron Lett.* **1992**, *33*, 2375–2378; (c) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron Lett.* **1994**, *35*, 3755–3758.
8. (a) Schinz, H.; Schäppi, G. *Helv. Chem. Acta* **1947**, *30*, 1483–1494; (b) Willimann, L.; Schinz, H. *Helv. Chem. Acta* **1949**, *32*, 2151–2164; (c) Eschenmoser, A.; Frey, A. *Helv. Chem. Acta* **1952**, *35*, 1660–1666.
9. Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4262–4263.
10. (a) House, H.; Wasson, R. L. *J. Am. Chem. Soc.* **1957**, *79*, 1488–1492; (b) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, *26*, 985–989; (c) Kunisch, F.; Hobert, K.; Welzel, P. *Tetrahedron Lett.* **1985**, *26*, 6039–6042; (d) Obuchi, K.; Hayashibe, S.; Asaoka, M.; Takei, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3206–3208.
11. Brown, H. C.; McFarlin, R. F. *J. Am. Chem. Soc.* **1958**, *80*, 3372–5376.
12. A unique example of such a chemoselective reduction is reported with only few details in Ref. 10c: β-ketoaldehyde **12e** gave β-ketoalcohol **8e** in 59% yield by treatment with $LiAlH(O\text{-}t\text{Bu})_3$ (1.06 equiv.) in THF (−65°C, 5.5 h).
13. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475–4478.
14. (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186; (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626; (c) Haseltine, J. N.; Paz Cabal, M.; Mautlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850–3866.
15. **Typical procedure** (Table 1, entry 3): synthesis of 7a-methyl-5,6,7,7a-tetrahydrocyclopenta[*c*]pyran-3(1*H*)-one **14c**. To a stirred solution at 0°C of diethylphosphonoacetic acid (1.6 g, 8.19 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was added DMAP (61 mg, 0.5 mmol) and 2-hydroxymethyl-2-methylcyclopentanone **8c** (0.7 g, 8.19 mmol). DCC (1.7 g, 8.19 mmol) was added at 0°C, and the reaction mixture was stirred at 20°C for 3 h. The precipitated urea was filtered off and the filtrate was evaporated in vacuo. The residue was taken up in $CH_2Cl_2$, the solution washed twice with 0.5N HCl, and with saturated

$NaHCO_3$ solution, and then dried over $MgSO_4$. The solvent was removed by evaporation and the ester **13c** isolated by flash-chromatography (silica, ether, $R_f = 0.1$) (1.3 g, 82%). To a solution of ester **13c** (930 mg, 3.04 mmol) and LiBr (846 mg, 9.73 mmol) in dry THF (10 mL) at 0°C under nitrogen was added $NEt_3$ (4.23 mL, 30.3 mmol). The reaction mixture was then stirred at room temperature for 3 h. The mixture was filtered through a plug of silica gel, washing with ethyl acetate. The filtrate was concentrated, and the residue purified by flash-chromatography (silica gel, PE/ether 6:4) to give lactone **14c** (320 mg, 70%). TLC ($SiO_2$, $R_f = 0.2$); IR ($CHCl_3$) 2940, 1740, 1460, 1220, 1140, 870, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (s, 3H), 1.42 (ddd, $^2J = 12.5$, $^3J = 8.5$, $^3J = 2.2$ Hz, 1H), 1.65 (ddd, $^2J = 12.5$, $^3J = 6.6$, $^3J = 2.6$), 1.80–2.05 (m, 2H), 2.52 (dtd, $^2J = 19.1$, $^3J = 8.5$, $^4J = 1.5$ Hz, 1H), 2.63 (dddd, $^2J = 19.1$, $^3J = 9.2$, $^3J = 4.8$, $^4J = 1.8$ Hz, 1H), 4.04 (d, $^2J = 10.7$ Hz, 1H), 4.24 (d, $^2J = 10.7$ Hz, 1H), 5.66 (dd, $^4J = 1.5$, $^4J = 1.8$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.4 (C-8), 22.4 (C-6), 26.7 (C-7), 35.7 (C-5), 42.1 (C-7a), 77.2 (C-1), 110.8 (C-4), 164.6 (C-4a), 174.1 (C-3); MS (70 eV): $m/z$ (%): 152 (4, $M^{+\bullet}$), 122 (33), 108 (20, $M^{+\bullet}-CO_2$), 93 (23), 79 (100), 65 (20), 51 (36), 39 (79). Anal. calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.77; H, 8.12.