anhydride (ca. 10 mL) for 30 min. The cold mixture was poured on 250 mL of ice water. A dark red oil was formed, which became solid after 24 h. The solid was collected and purified by preparative TLC (silica gel, 15:1 Cl_3CH/MeOH): yield 80%; mp 147–148 °C (from methanol–water); IR (KBr) 3660, 3520, 3360, 3260 (NH, H_2O), 2210 (CN), 1720 (C=O), 1630 (C=C) cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 10.8 (bs, 1 H, NH), 7.3–8.2 (m, 10 H arom), 2.1 (CH_3CO); mass spectrum, m/e 394 (M^+, 9), 352 (2), 308 (2), 281 (2), 209 (2), 106 (8), 105 (100), 77 (28). Anal. Calcd for $C_{23}H_{14}N_4O_3 \cdot 0.5H_2O$: C, 68.48; H, 3.75; N, 13.88. Found: C, 68.38; H, 3.70; N, 13.80.

Acknowledgment. Support of this work by a grant from the Comisiõn Asesora de Investigaciõn Científica y Técnica de la Presidencia del Bogierno of Spain (Grant PB86-0570) is gratefully acknowledged.

Registry No. 1, 1885-22-9; **2a**, 614-16-4; **2b**, 85692-25-7; **2c**, 4640-66-8; **3a**, 115437-98-4; **3b**, 115437-99-5; **3c**, 115438-00-1; **5a**, 115438-01-2; dibromomalononitrile, 1885-23-0.

Supplementary Material Available: Full X-ray data for **3a** (6 pages). Ordering information is given on any current masthead page.

Organomercury Chemistry of Iridoid Glucosides. 1. Chemoselective Hydroxymercuration–Demercuration of Aucubin: A Cheaper and Efficient Approach to Epimeric Isoeucommiols and 6,7-Bis(hydroxymethyl)-*cis*-2-oxabicyclo[3.3.0]oct-7-enes[1]

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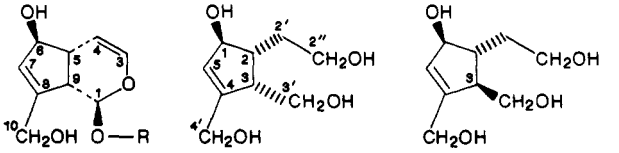
The utilization of iridoid glucosides, mainly of aucubin **1**, the most abundant and widespread member of this group, as chiral natural precursors for the synthesis of prostaglandins and other biologically active cyclopentanoid compounds has in recent years received considerable attention in our laboratory[3] and elsewhere.[4]

We recently reported[3f] the synthesis of a new intermediate for methyl jasmonate and the PG's from isoeucommiol **2**, a chiral cyclopentene tetrol, which was obtained[5] through expensive enzymatic hydrolysis (β-glucosidase) of **1** and $NaBH_4$ reduction of its aglycon **3** (aucubigenin).

Previously—by acid-catalyzed cyclization of **2**—we had obtained the 6α,7-bis(hydroxymethyl)-*cis*-2-oxabicyclo-[3.3.0]oct-7-ene **4**, precursor of modified PG's.[3a,b]

Taking advantage of the chemoselectivity of the hydroxymercuration–demercuration (OM–DM) reaction[6] toward the enol ether double bond of **1**, we have realized a more efficient and inexpensive synthesis of **2**, which led also to its unknown C-3 epimer **5**.

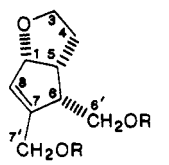
Compound **4** and its C-6 epimer **7** have also been obtained by this procedure. The stereochemistry of **7** renders it particularly useful for prostaglandin syntheses.



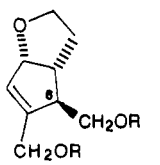
1, R = β-Gluc; **3**, R = H

2

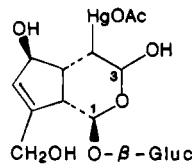
5



4, R = H



7, R = H



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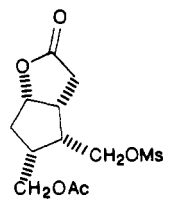

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Results and Discussion

In the course of our studies on the transformation of **2**[3f] we verified the unexpected unreactivity of its trisubstituted double bond toward the classical OM–DM procedure,[7a,b] even under different experimental conditions and in spite of literature reports on similar unsaturated systems.[7,8]

Failure of this attempt, however, paved the way for a chemoselective application of the OM–DM reaction to the direct transformation **1** → **2**, on the assumption that the Δ^7 double bond of **1** would be as unreactive as the identically substituted double bond of **2**.

Reaction of the enol ether double bond of **1** with $Hg(OAc)_2$ in THF–H_2O afforded the organomercurial **6** containing a new hemiacetal function at C-3. Successive reductive replacement of mercury by hydrogen ($NaBH_4$, DM stage) allowed reduction of hemiacetal functions at C-3 and at C-1 to CH_2OH groups with loss of the D-glucose moiety. The product[9] of this clean and high-yield (85%) reaction showed, in different eluents, an R_f value identical with that of isoeucommiol **2** prepared from aucubigenin **3**.[5]

As this new route to isoeucommiol **2** might allow a "one-pot" reaction for the patented conversion[3a,b] **1** → **2** → **4**, the OM–DM of **1** was repeated by acidifying the THF–H_2O solution obtained after filtration of Hg°. Unpredictably, two products were obtained with very close

(1) Abstracted in part from the "Dottorato di Ricerca" Thesis of Davini, E., University of Rome, 1984–86.

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(3) (a) Bonini, C.; Iavarone, C.; Trogolo, C.; Di Fabio, R. *J. Org. Chem.* **1985**, *50*, 958. (b) Bonini, C.; Iavarone, C.; Trogolo, C.; Di Fabio, R. Ital. Pat. Appl. 49042 A/81, 1981. (c) Davini, E.; Iavarone, C.; Trogolo, C.; Aureli, P.; Pasolini, B. *Phytochemistry* **1986**, *25*, 2420. (d) Bernini, R.; Davini, E.; Iavarone, C.; Trogolo, C. *J. Org. Chem.* **1986**, *51*, 4600. (e) Davini, E.; Iavarone, C.; Trogolo, C. *Phytochemistry* **1987**, *26*, 1449. (f) Davini, E.; Iavarone, C.; Trogolo, C. *Heterocycles*, **1988**, *27*, 87. (g) Davini, E.; Iavarone, C.; Mataloni, F.; Trogolo, C. *J. Org. Chem.* **1988**, *53*, 2089. (h) Davini, E.; Iavarone, C.; Trogolo, C. *Heterocycles* **1988**, *27*, 1557.

(4) See ref 3d and references therein.

(5) Bianco, A.; Guiso, M.; Iavarone, C.; Passacantilli, P.; Trogolo, C. *Tetrahedron* **1977**, *33*, 851.

(6) Although the first stage of this reaction is traditionally referred to as oxymercuration (hence the abbreviation OM), we shall use the more rigorous term hydroxymercuration in the text.

(7) (a) Brown, H. C.; Geoghegan, P. J., Jr. *J. Org. Chem.* **1970**, *35*, 1844. (b) Brown, H. C.; Geoghegan, P. J., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522. (c) Brown, H. C.; Lynch, G. J.; Hammar, W. J.; Liu, L. C. *J. Org. Chem.* **1979**, *44*, 1910. (d) Brown, H. C.; Hammar, W. J. *Tetrahedron* **1978**, *34*, 3405.

(8) Brown, H. C.; Lynch, G. J. *J. Org. Chem.* **1981**, *46*, 531.

(9) The ^1H NMR spectrum (300 MHz) of isolated product showed, besides the signals of **2**, the presence of additional low-intensity signals attributable to traces (10–20%) of a not separable contaminant, whose structure and formation will be explained later in this paper.

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GC retention times (t_R) and TLC R_f values which were separated by a careful chromatographic procedure. The most abundant (about 80%) and highest R_f product proved to be identical (R_f and t_R values, ^1H and ^{13}C NMR spectra) with 4,[3a] while the less abundant compound 7 (about 20%) showed some spectral differences, mostly evident in the ^{13}C NMR spectra. The marked deshielding of C-6 (+6.49 ppm), C-6′ (+2.57 ppm), and C-4 (+6.09 ppm) of 7 were in agreement with inversion ($\alpha \rightarrow \beta$) of the CH_2OH-6 configuration. That 4 and 7 were C-6 epimers was definitely proved by detailed spin decoupling experiments. In fact, by irradiating the multiplet at δ 3.63 (2H-6′) of 4, the broad quartet at δ 2.87 (H-6) was reduced to a doublet whose coupling constant ($J_{5,6}$ = 7.8 Hz; dihedral angle $\phi_{5,6}$ = ca. 5–10°), confirmed the α orientation of CH_2OH-6. On the contrary, irradiation of the octet at δ 3.53 (2H-6′) of 7, sharpened the broad signal at δ 2.60 (H-6) to a singlet ($\phi_{5,6}$ = ca. 90°, i.e. H-5 (β) and H-6 in *trans* arrangement), which implies a β configuration for CH_2OH-6 group.

The formation of 7 as by product of this acid-catalyzed reaction could be explained by assuming that the sample of isoeucommiol 2 obtained by OM–DM of 1 contained some 5 (3-*epi*-isoeucommiol) as a result of partial epimerization of the iridoidic C-9 center during the DM stage of 6. On the other hand, careful study of the cyclization with a sample of pure 2 obtained by the "enzymatic procedure" ($NaBH_4$ reduction of aucubigenin 3)[5] did not result in formation of 7 (and therefore of 5).

The different results from use of the same reducing agent may be ascribed to the different intermediates (3 and 6, respectively). The formation of 2 from aucubigenin 3[3c] involves direct attack of H^- on the α-oriented C-9 hemiacetal function, which is therefore immediately reduced without epimerization to α-oriented CH_2OH. On the other hand, in the DM method using 6, H^- attacks preferentially the new hemiacetal function at C-3. In this case, therefore, due to the basic medium, partial equilibration of the higher energy α-oriented intermediate to the thermodynamically more stable β configuration trans to the vicinal α side chain at C-5 might occur. In PG syntheses a like base-catalyzed epimerization of the C-12 formyl group is quite common.[10]

Thus 2 might be obtained by fast reduction of 6 under nonbasic conditions and 5 by slow reduction in a basic medium.[11] In fact, if the DM reaction of 6 was carried out in THF/KH_2PO_4 buffer at pH 5 with subsequent slow addition of this cold solution to a great excess of $NaBH_4$ in the same cold buffer (pH 5), 2 was obtained in high yield (89%) and purity, and it afforded 4 free from 7. On the other hand, the best results for synthesis of 5 from 6 were achieved by slowly adding a basic solution of $NaBH_4$ to the cooled, basified solution of organomercurial 6. Under these conditions the ratio of 5 to 2 was 4:1, determined as usual through GC analysis of the corresponding epimeric pair 7 and 4.

In conclusion, the amazing unreactivity of trisubstituted double bond of 2 toward OM–DM,[12] probably due to intrinsic factors (salts complexation and/or effect of nearby withdrawing oxygens[13]), allowed us to realize by OM–DM a more efficient and inexpensive transformation 1 → 2 → 4, patented[3a,b] route to PG intermediate 8 and to obtain from 1—through direct epimerization of C-9 center—the new chiral compounds 5 and 7, which are particularly suitable for PG syntheses.[14]

We are currently investigating the corresponding reaction of solvomercuration–demercuration of 1.

Experimental Section

General Procedures. General techniques have been described earlier.[3d] ^1H NMR: For spectra in D_2O the HDO signal (δ 4.70) was taken as internal standard with a probe temperature in the range 20.8–21.0 °C. Gas chromatographic analysis were carried out with a Hewlett-Packard 5880A instrument and a 10 m length capillar column OV 101.

Oxymercuration–Demercuration (OM–DM) of 1: Epimeric Mixture of Isoeucommiols 2–5 and Bicyclo Derivatives 4–7. To a stirred solution of mercuric acetate (1.0 g, 3.1 mmol)[15] in water (20 mL), THF (5.0 mL) was added to produce a yellow precipitate. Then 1[16] (1.0 g, 2.9 mmol) was added, and when all of the yellow suspension was vanished (few seconds), stirring was maintained for an additional 20 min, when a TLC ($CHCl_3$–MeOH, 7:3) showed the complete disappearance of 1 and the presence of a product at R_f 0 (organomercurial 6). After a portionwise addition of a $NaBH_4$ excess (0.8 g), TLC ($CHCl_3$–MeOH, 8:2) showed the formation of a product with the same R_f as 2. The mixture was stirred until all mercury had coagulated (1 h), and then the filtered solution was carefully bubbled with CO_2 until pH 8. Decolorizing charcoal was added, and the suspension was poured on a silica gel layer stratified in a Gooch funnel. The inorganic salts were totally eluted with water and, successively, the organic fraction with MeOH. Evaporation in vacuo of the MeOH and purification of the residue by column chromatography ("washed silica gel") in $CHCl_3$–MeOH, 85:15, gave seemingly pure 2 as an oil (472 mg, 85%), which was dissolved in 0.1 N HCl (6 mL) and left overnight at room temperature. TLC ($CHCl_3$–MeOH, 95:5) showed complete disappearance of 2 and formation of two less polar products with very close R_f values, the upper and more abundant compound having the same R_f value as 4. The aqueous solution was neutralized ($NaHCO_3$), transferred to a liquid–liquid extractor, and extracted with EtOAc (2 × 250 mL, 12 h). The EtOAc solution, dried (Na_2SO_4) and evaporated in vacuo, afforded a mixture of 4 and 7 (184 mg, $yield_{1\rightarrow 4+7}$ = 75%) in GC ratio 4:1. Chromatographic separation ("washed silica gel") with $CHCl_3$–MeOH, 9:1, gave pure 4 (118 mg), a 1:1 mixture of 4 and 7 (36 mg) and finally pure 7 (17 mg).

OM–DM of 1: Isoeucommiol 2 and Bicyclo Derivative 4. To a stirred solution of mercuric acetate (0.5 g, 1.57 mmol) in KH_2PO_4 buffer (5 M) at pH 5.0 (10 mL) was added THF (2.5 mL). To the yellow suspension was added 1 (0.5 g, 1.45 mmol). After 20 min the colorless solution, cooled at 0 °C, was added dropwise with stirring to a cooled (0 °C) solution of $NaBH_4$ (0.2 g) in the same buffer (15 mL). After 15 min the reaction mixture was checked (TLC) and worked up as before, up to isolation of 2 (242 mg, 89%) whose ^1H NMR spectrum was superimposable on the one of authentic 2 (from "enzymatic way").[5] Successive cyclization of 2 in 0.1 N HCl (3 mL) led to the exclusive formation of 4 (TLC and GC shows the absence of 7). After the usual workup, pure 4 (192 mg, $yield_{1\rightarrow 4}$ = 76%) was obtained. ^1H NMR (300 MHz, D_2O): δ 5.52 (br s, 1 H, H-8), 4.97 (d, 1 H, H-1, $J_{1,5}$ = 7.8 Hz), 4.04 (dd, 2 H, 2 H-7′, J_{AB} = 15.0 Hz), 3.74–3.51 (cm, 2 H, 2 H-3), 3.63 (cm, 2 H, 2 H-6′), 3.01 (p, 1 H, H-5, J = 7.8 Hz), 2.87 (br q,

(10) (a) Naruto, M.; Ohno, K.; Naruse, N. *Chem. Lett.* **1978**, 1419. (b) Brewster, D.; Myers, M.; Ormerod, J.; Otter, P.; Smith, A. C. B.; Spinner, M. E.; Turner, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2796. (c) Crabbé, P.; Cervantes, A.; Meana, M. C. *J. Chem. Soc., Chem. Commun.* **1973**, 119. (d) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.

(11) Owing to the difficulty in separating epimers 2 and 5, the verification of this working hypothesis had to be done indirectly by testing their acid-catalyzed conversion into corresponding bicyclo derivative epimers 4 and 7.

(12) We tested unsuccessfully different ratios of THF–water and Hg^{2+} salts–2 as well as different Hg^{2+} salts like $Hg(OAc)_2$, $Hg(NO_3)_2$, and $HgCl_2$, either at room temperature or under refluxing (the formation of 4 by using $Hg(NO_3)_2$ was clearly attributable to the acidic conditions).

(13) This explanation also reflects Prof. R. C. Larock's (Iowa University) opinion (private communication).

(14) (a) Robinson, G. E. Ger. Offen. 2633559, 1975; *Chem. Abstr.* **1977**, *86*, 170942. (b) Kienze, F.; Rosen, P. U.S. Pat. 4 044 055 1977; *Chem. Abstr.* **1978**, *88*, 74110. (c) Yankee, E. W. Ger. Offen. 2719975, 1977; *Chem. Abstr.* **1978**, *88*, 62048.

(15) The cyclopentene double bond of 1 retains its unreactivity even with higher excess of $Hg(OAc)_2$.

(16) Twenty grams of 1 were obtained[3g] from 1 kg of fresh leaves of common shrub *Aucuba japonica*.

1 H, H-6), 1.76 (q, 2 H, 2 H-4, J = 7.8 Hz).

OM–DM of 1: 3-*epi*-Isoeucommiol 5 and Bicyclo Derivative 7. To the yellow suspension obtained by adding THF (2.5 mL) to a stirred solution of mercuric acetate (0.5 g, 1.57 mmol) in water (10 mL) was added 1 (0.5 g, 1.45 mmol). After 20 min, to the colorless solution, cooled at 0 °C, was added 6 N NaOH (5 mL), and then, slowly and under stirring, 0.5 M $NaBH_4$ solution (15 mL) in 2 N NaOH was added. After 15 min the reaction mixture was worked up as before to give a mixture **2–5** (236 mg, 87%). Successive addition of 0.1 N HCl (3 mL) gave, after usual workup, a mixture of **7** and **4** (191 mg, yield$_{1\rightarrow 7+4}$ = 78%) in GC ratio 4:1. Chromatographic separation ("washed silica gel") with $CHCl_3$–MeOH, 9:1, afforded pure **4** (14 mg), a 1:1 mixture of **4** and **7** (42 mg), and finally pure **7** (120 mg). ^{1}H NMR (300 MHz, D_2O): δ 5.54 (br s, 1 H, H-8), 4.99 (d, 1 H, H-1, $J_{1,5}$ = 7.8 Hz), 4.06 (dd, 2 H, 2 H-7′, J_{AB} = 15.0 Hz), 3.71–3.52 (cm, 2 H, 2 H-3), 3.53 (o, 2 H, 2 H-6′), 2.69 (cm, 1 H, H-5), 2.60 (br s, 1 H, H-6), 2.04–1.92 and 1.65–1.56 (cm, 2 H, 2 H-4). ^{13}C NMR (D_2O): δ 150.19 (s, C-7), 126.30 (d, C-8), 88.16 (d, C-1), 66.87 (t, C-3), 63.91 (t, C-6′), 59.89 (t, C-7′), 55.03 (d, C-6), 45.17 (d, C-5), 34.13 (t, C-4).

The above procedure, leading to the selective preparation of bicyclo derivatives **4** and **7**, could be shortened by starting from the Hg° filtration. The filtered solution was directly acidified with HCl (initially 6 N and then 2 N) until pH 3–4 (Congo Red). After being stirred overnight, the aqueous solution was neutralized with $NaHCO_3$ and then extracted in a liquid-liquid extractor with EtOAc (2 × 250 mL, 12 h). The EtOAc solution, dried (Na_2SO_4) and evaporated in vacuo, afforded the desired bicyclo derivative, which was purified as described.

Registry No. 1, 479-98-1; 2, 64274-29-9; 3, 64274-28-8; 4, 94707-63-8; 5, 116050-15-8; 6, 116004-75-2; 7, 116050-16-9.

Direct Lithiation of Hydroxyaromatics

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Since the pioneering work of Gilman and Wittig almost 50 years ago,[1] aromatic lithiation[2] has evolved as a powerful method for the introduction of a wide variety of functional groups and alkyl side chains at positions not easily available by other means (i.e. electrophilic aromatic substitution).

Though the mechanistic pathway for the heteroatom-facilitated lithiation is poorly understood, it is generally believed that coordination of the incoming lithium base with the available coordinating groups takes place prior to the actual hydrogen–lithium exchange step.[3] Accordingly, phenoxides are generally considered very poor ortho directors in metalation reactions, although it has been recently demonstrated that the direct metalation of phenol itself (ortho to the OH group) can be worked out by using the appropriate selection of reagents (*t*-BuLi/THP).[4] Moreover, in our recent work toward the synthesis of

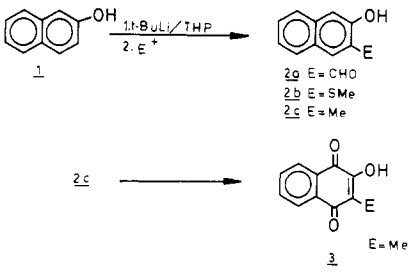

Figure 1.

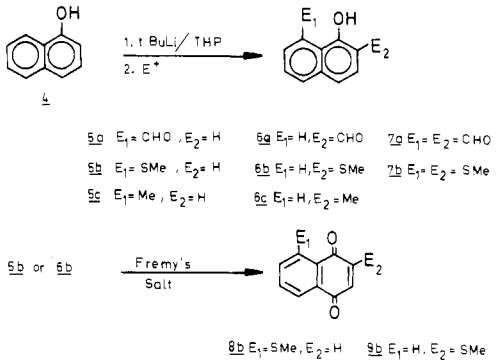

Figure 2.

quinones, we have been able to prove that substituted phenols can be metalated in a regioselective manner (ortho to other directors other than the OH group) by the action of *t*-BuLi/THP or, in appropriate cases, by *n*-BuLi/THF.[5]

Continuing with our efforts in the field, we now report our work on the direct lithiation of polycyclic aromatic systems containing an OLi group as the only directing group, namely, the lithium salts of naphthols, anthranols, and also some polyphenols. The major objective of our plan was to achieve the regioselective introduction of electrophiles onto mono and polyhydroxy benzenes, naphthalenes, and anthracenes. Obviously, if this goal were reached, a powerful methodology for the regioselective preparation of a variety of substituted polycyclic aromatics and many simple derivatives such as the corresponding quinones would be at hand.

In the event, direct lithiations were carried out under standard conditions, i.e. by operating with 25% M excess of *t*-BuLi, which was added in ca. 2 min to a concentrated solution (2 M) of the substrate in anhydrous tetrahydropyran,[6] at room temperature (see the Experimental Section). By so doing, a strongly exothermic reaction (to ca. 50 °C) takes place. It is worth noting in this context that running the reaction at lower temperature, decreasing the rate of addition of *t*-BuLi (15 min instead of 2 min), or working with more dilute solutions of either substrate (≤1 M) or lithium base (≤1.7 M) led to a significant decrease in yield of the final product and the subsequent recovery of unchanged starting material.

Treatment of 2-naphthol (1) under the above working conditions led to a viscous paste, which was then quenched with different electrophiles, namely DMF, $(MeS)_2$, MeI,

(1) (a) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109. (b) Wittig, G.; Furhman, G. *Chem. Ber.* **1940**, *73*, 1197.

(2) Gilman, H.; Morton, J. W. *Org. React.* (*N.Y.*) **1954**, *8*, 258. Gschwend, H. W.; Rodriguez, H. *Org. React.* (*N.Y.*) **1979**, *26*, 1. Wakefield, B. J. *Organolithium* Compounds; Pergamon: New York, 1974. Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

(3) Barnes, R. A.; Nehmsmann, L. J. *J. Org. Chem.* **1966**, *27*, 1939. See also ref 2.

(4) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571.

(5) Saâ, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1986**, *27*, 5125. Costa, A.; Saâ, J. M. *Tetrahedron Lett.* **1987**, *28*, 5551. Saâ, J. M.; Llobera, A.; Garcia-Raso, A.; Costa, A.; Deyâ, P. M. *J. Org. Chem.*, in press.

(6) THP is, at least partially, destroyed by the action of *t*-BuLi. It is premature to determine whether or not the resulting alkoxide plays a major role on the reaction mechanism by reacting with the organolithium derivatives present. See: Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. Schlosser, M.; Strunck, S. *Tetrahedron Lett.* **1984**, *25*, 741 and references therein.

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