cussion and invaluable suggestions. H.-w.L. also thanks the National Institutes of Health for a Research Career Development Award (GM 00559).

Registry No. 3, 125827-35-2; 4, 57044-25-4; 5a, 12327-62-7; 5b, 16495-13-9; 6, 73476-18-3; 7a (diastereomer-1), 139242-75-4; 7a (diastereomer-2), 139344-59-5; 7b (diastereomer-1), 139242-76-5; 7b (diastereomer-2), 139344-60-8; 8a (diastereomer-1), 139242-77-6; 8a (diastereomer-2), 139344-61-9; 8b (diastereomer-1), 139242-78-7; 8b (diastereomer-2), 139344-62-0; 9a (diastereomer-1), 139242-79-8; 9a (diastereomer-2), 139344-63-1; 9b (diastereomer-1), 139242-80-1; 9b (diastereomer-2), 139242-81-2; 10, 139242-82-3; 10 (MTPA ester), 136060-96-3; 11 (diastereomer-1), 139242-83-4; 11 (diastereomer-2), 139344-64-2; 12 (diastereomer-1), 139242-84-5; 12 (diastereomer-2), 139344-65-3; 13 (diastereomer-1), 139242-85-6; 13 (diastereomer-2), 139344-66-4; 14, 139242-86-7; MTPA, 56135-03-6; TBDMS-Cl, 18162-48-6; $PhCH_2Br$, 100-39-0; CH_2=$CHSiMe_3$, 754-05-2; PhSH, 108-98-5; $Me_3SiCH_2CH_2SPh$, 17988-59-9.

Supplementary Material Available: Spectra of 5-14 (38 pages). Ordering information is given on any current masthead page.

Lewis Acid Induced Homoallylic C-Alkylation. 2.[1] Application to the Synthesis of Unsaturated Diketo *C*-Glycosides. Mechanistic Aspect of the Reaction

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Keto unsaturated glycosides play a pivotal role as building blocks in organic synthesis.[2] Moreover, these molecules have attracted an increasing interest recently with the discovery of the antitumor properties of keto unsaturated *N*- and *C*-glycosides.[3,4] We are currently engaged in studies directed toward the synthesis of complex unsaturated *C*-glycosides[1,5,6] and their use as building blocks in the synthesis of naturally occurring antitumoral compounds.[7] Among these molecules β-substituted keto unsaturated *C*-glycosides are of special interest because they are potent key intermediates for the synthesis of important synthetic targets with a framework of β-substituted tetrahydropyran like quasinoids and tricothecanes (Figure 1). This type of *C*-glycoside should be readily available by a Cr(IV) oxidative rearrangement of a tertiary allylic alcohol prepared from dioxo unsaturated *C*-glycosides.

The syntheses of *C*-glycosides by way of CC bond formation between a peracetylated glycal and a nucleophilic

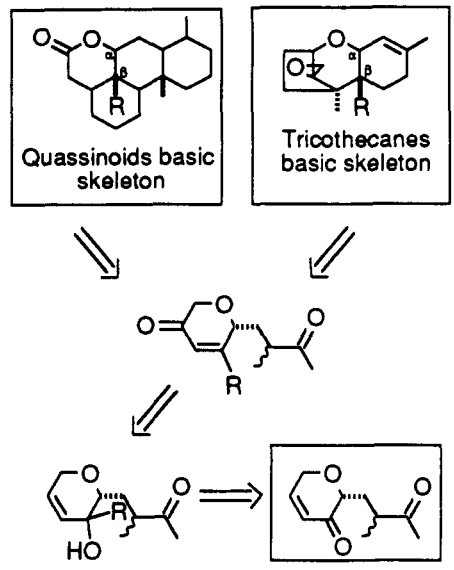

Figure 1.

reagent draw considerable attention in recent years.[8-10] However, only our olefin-based methodologies[1,5,6] allow the direct generation of 2-keto unsaturated C-glycosides.[6] Herein we report the first preparation of keto and aldehydo 2*H*-pyran-3-ones by the reaction of peracetylated 2-hydroxy glycals with silyloxy allylic ethers. This process avoids the deprotection of enol esters that requires multistep reactions[11] or processes not always compatible with the stability of the glycosides.[12]

Our results are summarized in Table I. The coupling of tri-*O*-acetyl-2-hydroxy-L-fucal (1) and [(thexyldimethylsilyl)oxy]-3-methyl-3-buten-2-ol (2) was chosen as a model system. After examining the effect of a variety of catalytic systems ($ZnBr_2$, $SnCl_4$, $SnBr_4$, $TiCl_4$, $FeCl_3/SiO_2$, $BF_3{\cdot}Et_2O$, $SnBr_4/SnCl_4$ 4-Å molecular sieves, $ZnBr_2$ ultrasound) we arrived at the following optimal procedure. Glycal 1 (5-10 mmol) and thexyldimethylsiloxy ether 2 (1.2 equiv) was added dropwise to a stirred suspension of 4-Å molecular sieves and dry zinc bromide (1 equiv) in dichloroethane under ultrasound at 15 °C. After 5 h the *C*-glycoside 3 was isolated in 72% yield (Table I, entry 1). The enone structure of 3 was dictated by the conjugated olefinic resonances at δ_H 6 and 6.9 ppm and by the carbonyl signal at δ_C 212.06 ppm.

With a good catalytic system at hand we extended the reaction to various glycals. Table I shows clearly that the reaction was dependent on the substitution at C-6. Thus,

(1) For part 1 see: Herscovici, J.; Delatre, S.; Antonakis, K. *J. Org. Chem.* **1987**, *52*, 5691.
(2) Holder, N. L. *Chem. Rev.* **1982**, *82*, 287.
(3) Antonakis, K. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; p 221.
(4) Herscovici, J.; Bennani-Baiti, M. I.; Frayssinet. C.; Antonakis, K. *Biomed. Chem. Lett.* **1991**, *1*, 395. (b) Herscovici, J.; Bennani-Baiti, M. I.; Montserret, R.; Frayssinet. C.; Antonakis, K. *Biomed. Chem. Lett.* **1991**, *1*, 721.
(5) Herscovici, J.; Muleka, K.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 5653.
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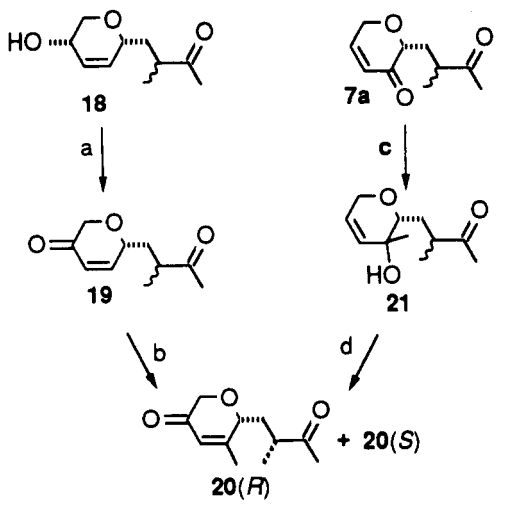
(7) Herscovici, J.; Delatre, S.; Antonakis, K. *Tetrahedron. Lett.* **1991**, *32*, 1183.
(8) (a) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 111; (b) Daves, G. D., Jr.; Cheng, C. C. *Prog. Med. Chem.* **1976**, *13*, 303. (c) Buchanan, J. G. *Prog. Chem., Org. Nat. Prod.* **1983**, *44*, 243. (d) Daves, G. D., Jr.; *Acc. Chem. Res.* **1990**, *23*, 201.
(9) For palladium assisted alkylation see: (a) Cheng, J. C. Y.; Daves, G. D., Jr.; *Organometallics* **1986**, *5*, 1753. (b) Cheng, J. C. Y.; Daves, G. D. Jr.; *J. Org. Chem.* **1987**, *52*, 3083. (c) Czernecki, S.; Gruy, F. *Tetrahedron. Lett.* **1981**, *22*, 437. (d) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533. (e) Gillier-Pandraud, H.; Brahmi, R.; Bellosta-Dechavanne, V.; Czernecki, S. *Can. J. Chem.* **1985**, *63*, 491. (f) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642. (g) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812. (h) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89. (i) Yougai, S.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 68. (j) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890 and references cited therein.
(10) (a) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522. (b) Grynkiewicz, B.; BeMiller, J. *J. Carbohydr. Chem.* **1982**, *1*, 121. (c) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803. (d) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.
(11) Lichtenthaler, F. W.; Jarglis, P. *Tetrahedron Lett.* **1980**, *21*, 1425.
(12) (a) Anet, E. F. L. J. *Carbohydr. Res.* **1966**, *1*, 348. (b) Bock, K.; Pedersen, C. *Tetrahedron Lett.* **1969**, 2983.

0022-3263/92/1957-2476$03.00/0

Scheme I[a]



[a] Reagents: (a) PDC/4-Å MS (72%); (b) Me_2CuLi, TMSCl, $Pd(OAc)_2$, (60%); (c) MeLi, −100 °C (70%); (d) PCC/4-Å MS.

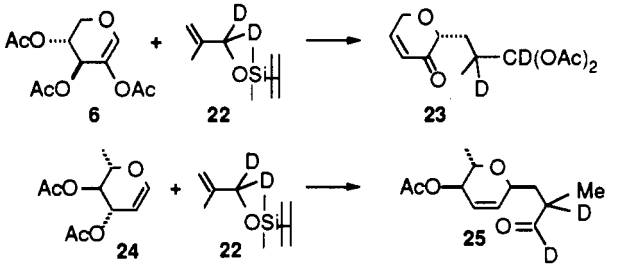
alkylation of triacetyl 2-hydroxy-D-xylal (**6**) led to a mixture of two products. The major one was identified as the diketo *C*-glycoside **7a** (71% yield). The minor compound was identified as the 1,1-bis(acetyloxy) 2,2-dimethyl *C*-glycoside **7b** (entry 3). Peracetylated 2-hydroxy-L-xylal **8** led also to a mixture containing the diketo *C*-glycoside **9a** (70%) and the bis(acetyloxy) acetal **9b** (10%) (entry 4). Condensation among **2** and the peracetylated 2-hydroxy glucal **4** led to poor results ($ZnBr_2$, sonochemistry). However, **5** could be prepared in fair yield (53%) using a mixture of $SnBr_4$ and $SnCl_4$ in the presence of 4-Å molecular sieves at 0 °C for one night (entry 2).

Condensation of [(thexyldimethylsiloxy)oxy]-2-methyl-2-propen-1-ol (**10**) with 2-(acetyloxy)glycal **1** using zinc bromide under sonochemical conditions did not led to the expected aldehydo *C*-glycoside. Instead the reaction gave the 1,1-bis(acetyloxy) acetal **11** as evidenced by the acetyl resonances at δ 2.1 ppm and by the H-1 signal at δ 6.75 (d, 1 H, J = 3.34 Hz). Again reaction yields were dependent on the substitution at C-6. Condensation of **10** with glycals **6** and **8** produced the corresponding 2-keto *C*-glycosides **13** and **14** in 70% yield (entries 7 and 8). On the other hand penta-*O*-acetyl-2-hydroxy-D-glucal (**4**) afforded an unresolvable mixture of aldehyde **12a** and bis(acetyloxy) acetal **12b** (55% yield) (entry 6). However aldehydo *C*-glycosides could be prepared directly when the reaction was performed in the presence of an aldehyde. Thus alkylation of **1** in the presence of benzaldehyde (entry 9) gave the aldehydo *C*-glycoside **15** in 53% yield. Aldehydo *C*-glycosides **16** and **17** were prepared in the same fashion.

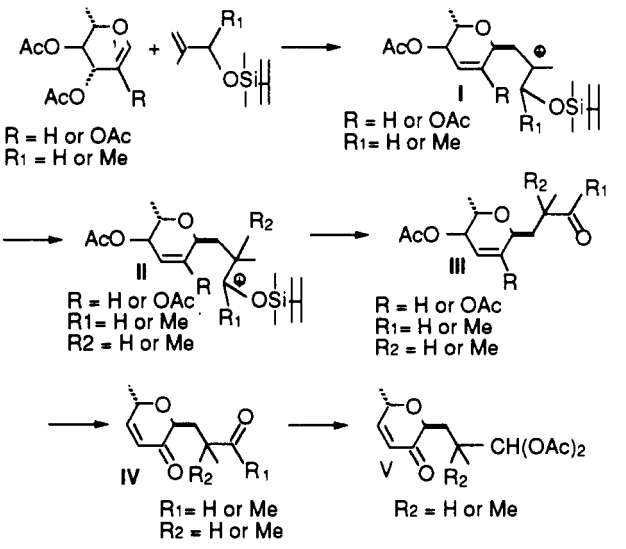
Table I shows the excellent stereoselectivity of the addition at the anomeric center. All the reactions led to α-*C*-glycosides. Assignment of configuration for the hexopyranose *C*-glycosides was performed using 2D NOESY spectra and optical rotation as it was previously reported.[6]

Pentopyranosyl *C*-glycoside assignment was not possible using spectroscopic and optical methodologies. To establish the configuration at the anomeric center the following experiments were done (Scheme I). First the dioxo *C*-glycosides **20**(*R*) and **20**(*S*) were prepared in two steps from the *C*-glycoside **18**[7] ((a) PDC/4-Å MS, 72%; (b) Me_2CuLi TMSCl, $Pd(OAc_2)$). Next, **7a** was chemoselectively transformed (MeLi, −100 °C) into the allylic tertiary alcohol (**21**). Oxidation of **21** (PCC/4-Å MS) afforded a mixture of the dioxo *C*-glycosides contaminated with an unknown compound. From this mixture only one diastereoisomer could be isolated in pure form that was found to be identical to **20**(*R*) $[\alpha]^{20}_D$ = +5° (*c* 0.1, methanol) indicating that the condensation of silyloxy allylic ether with peracetylated 2-hydroxyxylal yields α-*C*-glycosides.

Scheme II. Reactions of Glycals with Deuterated Silyloxy Ether



Scheme III



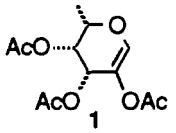
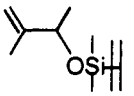
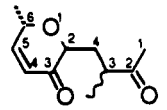
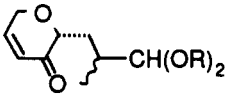
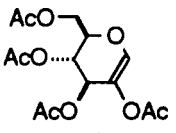
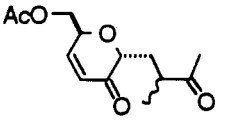
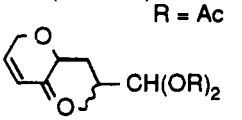
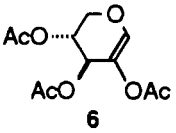
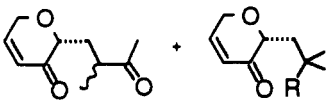
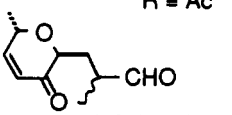
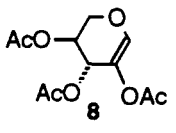
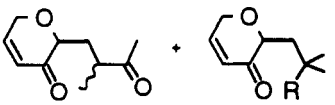
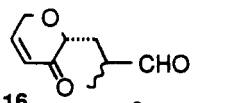
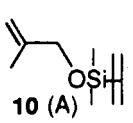
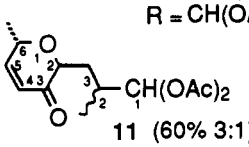
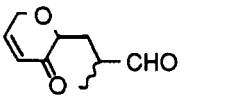
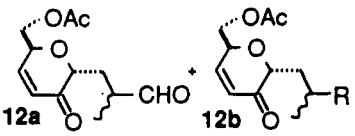
The minor formation of the dimethyl derivatives **7b** and **9b** suggested strongly a pinacol-like transposition mechanism for the allylic alcohol condensation. To demonstrate the soundness of this hypothesis for both primary and secondary silyloxy ethers, tri-*O*-acetyl-2-hydroxy-D-xylal (**6**) was condensed with [(thexyldimethylsilyl)oxy]-1,1-dideuterio-2-methyl-2-propen-1-ol (**22**) (Scheme II). As expected we isolated only the [*R*-(*R**,*R**,*S**)]-1,1-bis(acetyloxy)-1,2-dideuterio-α-methyl-2*H*-pyran-3(6*H*)-one-2-propanal (**23**). In the same fashion the dideuterio *C*-glycoside **25** was synthesized by the reaction of **22** with di-*O*-acetyl-L-rhamnal (**24**).

A mechanism that rationalizes the formation of deuterated products and that is consistent with all the data is outlined in Scheme III. Carbocation I produced by the olefin attack of the glycal at C-1 by an Sn2′ mechanism is the probable key intermediate of the process. Proton or methyl 1,2 shift followed by the rearrangement of the resulting carbocation II afforded the carbonyl derivative III. The 2-(acetyloxy) derivatives undergo an acetolyis of the enol esters[6] with formation of the enones IV. Finally aldehydo oxo *C*-glycoside esterification led to the bis(acetyloxy) derivatives V.

Experimental Section

NMR spectra were recorded with a Bruker MSL 300 at 300.13 MHz (proton) and 75.37 MHz (carbon) with tetramethylsilane as internal standard. Microanalyses were performed by the Laboratoire central de Microanalyse du CNRS, Vernaison France.

Table I. Preparation of Unsaturated 2-Keto *C*-Glycosides from Glycals and (Thexyldimethylsilyl)oxy Ethers

entry	2-hydroxy glycals	silyloxy ethers (methods)	2-oxo C-glycosides (yield % *S:R*)	entry	2-hydroxy glycals	silyloxy ethers (methods)	2-oxo C-glycosides (yield % *S:R*)
1	 **1**	 **2** (A)	 **3** (72% 6:4)	7	**6**	**10** (A)	 **13** (70% 1:1) R = Ac
2	 **4**	**2** (B)	 **5** (53% 38/62)	8	**8**	**10** (A)	 **14** (70% 1:1) R = Ac
3	 **6**	**2** (A)	 **7a** (71% 1:2) **7b** (14%) R = $CH(OAc)_2$	9	**1**	**10** (C)	 **15** (53% 1:1)
4	 **8**	**2** (A)	 **9a** (70% 7:3) **9b** (10%) R = $CH(OAc)_2$	10	**6**	**10** (C)	 **16** (66.5%[a] 1:1)
5	**1**	 **10** (A)	 **11** (60% 3:1)	11	**8**	**10** (C)	 **17** (70%[a] 1:1)
6	**2**	**10** (B)	 **12a** **12a** + **12a** 55% **12b** R = $CH(OAc)_2$				

[a] In some cases the aldo *C*-glycoside was contaminated with 1,2,4-tri-*O*-acetyl-1,5-anhydropent-2-enopyranosides (3–7%).

Tetracetyl-2-hydroxy-D-glucal,[13] triacetyl-2-hydroxy-L-fucal,[14] triacetyl-2-hydroxy-D-xylal,[14] triacetyl-2-hydroxy-L-xylal,[14] [(thexyldimethylsilyl)oxy]-2-methyl-2-propen-1-ol,[15] and [(thexyldimethylsilyl)oxy]-3-methyl-3-buten-2-ol[15] were prepared according to published procedures. 1,1-Dideuterio-2-methyl-2-propen-1-ol was synthesized by the reduction of ethyl methacrylate with $LiAlD_4$. Dichloromethane was distilled from P_2O_5 and stored over 4-Å molecular sieves. Flash chromatography was carried out on silica gel 60 (30–60 μm) in the indicated solvents. Thin-layer chromatography was performed on silica gel 60 F254 (E. Merck). Optical rotations were measured on a Roussel-Jouan "Quick" polarimeter. Ultrasound assisted reactions were performed in an ultrasonic cleaner. Molecular sieves (4 Å) were dried over P_2O_5 for 1 h under vacuum (12 mm) at 500 °C.

Procedure for the Condensation of Olefins with Peracetylated Glycals. Procedure A. To a stirred suspension of 4-Å molecular sieves (0.7 g/mmol) and dry zinc bromide (1 equiv) in dichloroethane (1.5 mL/mmol) was added dropwise under ultrasound a mixture of glycal (5–10 mmol) and thexyldimethylsiloxy ether (1.2 equiv). When all the starting material had disappeared (4–6 h) the reaction was diluted with diethyl ether (15 mL/mmol) and then filtrated on Celite. The filtrate was successively washed with a saturated solution of $NaHCO_3$ (3 × 2 mL/mmol) and brine (2 mL/mmol) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure then flash chromatography in the indicated solvents furnished the pure *C*-glycosides.

Procedure B. A round-bottom flask equipped with a magnetic stirring bar was filled successively with glycal (3–6 mmol), dichloroethane (1.5 mL/equiv) molecular sieves (0.8 g/mmol), (thexyldimethylsilyl)oxy ether (1.2 equiv), and tin(IV) bromide (1 equiv). After 0.15 h the reaction mixture was cooled to 0 °C, and then tin(IV) chloride (1 equiv 1 M in dichloromethane) was added. After a night of stirring at 0 °C the suspension was poured in a 1:1 mixture of diethyl ether and a saturated solution of Na_2HPO_4 (10 mL/mmol). The aqueous layer was extracted twice with diethyl ether (5 mL/mmol). The organic layer was washed with a saturated solution of $NaHCO_3$ (5 mL/mmol) and with water (5 mL/mmol) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and then flash chromatography in the indicated solvents furnished the pure 2-oxo C-glycosides.

Procedure C. To a stirred suspension of 4-Å molecular sieves (0.7 g/mmol), benzaldehyde (3 equiv), and dry zinc bromide (1 equiv) in dichloroethane (1.5 mL/mmol) was added dropwise under ultrasound a mixture of glycal (3–6 mmol) and thexyldimethylsiloxy ether (1.2 equiv). When all the starting material had disappeared (3–5 h) the reaction was diluted with diethyl ether (15 mL/mmol) and then filtrated on Celite. The filtrate was successively washed with a saturated solution of $NaHCO_3$ (3 × 2 mL/mmol) and brine (2 mL/mmol) and then dried (MgSO4). The solvent was evaporated under reduced pressure, and then flash chromatography in the indicated solvents furnished the pure C-glycosides.

[2*S*-[2α(*R,*S**),6β]]-3-Methyl-4-[3,6-dihydro-6-methyl-3-oxo-2*H*-pyran-2-yl]-2-butanone (3):** 72% (hexane–ethyl ace-

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tate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = +67.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, *J* = 7 Hz, Me C-3), 1.32 (d, 1.8 H, *J* = 6.9 Hz, Me C-6 (*S*)), 1.38 (d, 1.2 H, *J* = 6.9 Hz, Me C-6 (*R*)), 1.65 (ddd, 0.6 H, *J* = 3.45, 5.76, and 14.30 Hz, H-4 (*S*)), 1.8 (ddd, 0.4 H, *J* = 4.89, 8.9, and 14.30 Hz, H-4 (*R*)), 2.17 (m, 0.4 H, H-4(*R*)), 2.18 (s, 1.8 H, H-1 (*S*)), 2.22 (s, 1.2 H, H-1 (*R*)), 2.25 (m, 0.6 H, H-4 (*S*)), 2.75 (m, 1 H, H-3), 4.2 (m, 1 H, Py H-2)), 4.5 (m, 1 H, H-6), 6.0 (dd, 1 H, *J* = 2.3 and 10.36 Hz, Py H-4), 6.9 (dd, 1 H, *J* = 2.59 and 10.36 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 16.68 and 17.13 (q, Me C-3), 18.37 and 19.34 (q, Me C-6), 28.52 and 28.97 (q, C-1), 32.12 and 32.42 (t, C-4), 42.92 and 44.14 (d, C-3), 65.56 (d, C-6), 76.75 (d, Py C-2), 124.91 (d, Py C-4), 151.66 and 152.34 (d, C-5), 196.22 (s, Py C-3), 212.06 (s, C-2). Anal. Calcd for $C_{11}H_{16}O_3 \cdot 0.5H_2O$: C, 64.36; H, 8.23. Found: C, 64.40; H, 8.13.

[2*R*-[2α(*R,*S**),6β]]-4-[6-[(Acetyloxy)methyl]-3,6-dihydro-3-oxo-2*H*-pyran-2-yl]-3-methyl-2-butanone (5)**: 53% (hexane–ethyl acetate (1:1)); $[\alpha]^{20}_D$ = −25° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.16 (d, 1.86 H, *J* = 7.02 Hz, Me C-3 (*R*)), 1.18 (d, 1.14 H, *J* = 6.91 Hz, Me C-3 (*S*)), 1.64 (ddd, 0.62 H, *J* = 3.45, 5.18, and 14.48 Hz, H-4 (*R*)), 1.78 (ddd, 0.38 H, *J* = 4.89, 8.64, and 14.36 Hz, H-4 (*S*)), 2-2.1 (m, 0.38 H, H-4 (*S*)), 2.1 (s, 3 H, CH_3CO), 2.2 (s, 3 H, H-1), 2.2–2.3 (m, 0.62 H, H-4 (*R*)), 2.75 (m, 1 H, H-3), 4.15 (dd, 0.62 H, *J* = 4.08 and 11.82 Hz, $AcOCH_2$ (*R*)), 4.22 (dd, 0.38 H, *J* = 3.94 and 11.82 Hz, $AcOCH_2$ (*S*)), 4.23 (m, 1 H, Py H-2), 4.32 (dd, 0.62 H, *J* = 6.49 and 11.82 Hz, 6-$AcOCH_2$ (*R*)), 4.37 (dd, 0.38 H, *J* = 5.95 and 11.82 Hz, $AcOCH_2$ (*S*)), 4.55 (m, 0.62 H, H-6), 4.63 (m, 0.38 H, H-6), 6.16 (dd, 0.38 H, *J* = 2.18 and 10.65 Hz, Py H-4 (*S*)), 6.17 (dd, 0.62 H, *J* = 2.18 and 10.65 Hz, Py H-4 (*R*)), 6.88 (dd, 0.38 H, *J* = 2.6 and 10.65 Hz, H-5 (*S*)), 6.92 (dd, 0.38 H, *J* = 2.6 and 10.65 Hz, H-5 (*R*)); ^{13}C NMR ($CDCl_3$) δ 17.17 (q, Me C-3), 20.01 (q, CH_3O), 29.08 (q, C-1), 32.15 and 32.58 (t, C-4), 42.86 and 44.21 (d, C-3), 63.46 and 64.17 (d, C-6), 67.85 and 69.07 (t, $AcOCH_2$), 75.73 and 76.67 (d, Py C-2), 127.12 and 127.42 (d, Py C-4), 145.83 and 146.80 (d, C-5), 170.64 (s, CH_3CO), 195.45 (s, Py C-3), 211.96 (s, C-2). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.16; H, 7.18.

[*R*-[*R,*R**,*S**]]-3-Methyl-4-[3,6-dihydro-3-oxo-2*H*-pyran-2-yl]-2-butanone (7a)**: 71% (hexane–ethyl acetate–dichloromethane (27.5:22.5:50)); $[\alpha]^{20}_D$ = +42.5° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (d, 2 H, *J* = 7.03 Hz, Me C-3 (*R*)), 1.15 (d, 1 H, *J* = 7.12 Hz, Me C-3 (*S*)), 1.77 (ddd, 0.33 H, *J* = 4.29, 8.38 and 14.55 Hz, H-4 (*S*)), 1.91 (ddd, 0.66 H, *J* = 3.74, 6.78 and 14.55 Hz, H-4 (*R*)), 2.1 (ddd, 0.66 H, *J* = 7.5, 9.79 and 14.55 Hz, H-4 (*R*)), 2.18 (s, 3 H, H-1), 2.36 (ddd, 0.33 H, *J* = 4.19, 9.24, and 14.55 Hz, H-4 (*S*)), 2.75 (m, 1 H, H-3), 4 (m, 1 H, Py H-2), 4.36 (m, 2 H, H-6), 6.11 (dd, 0.66 H, *J* = 2.10 and 10.66 Hz, Py H-4(*S*)), 6.13 (dd, 0.33 H, *J* = 2.15 and 10.33 Hz, Py H-4 (*R*)), 7.02 (dd, 0.33 H, *J* = 2.65 and 10.33 Hz, H-5 (*S*)), 7.06 (dd, 0.66 H, *J* = 2.65 and 10.66 Hz, H-5 (*R*)); ^{13}C NMR ($CDCl_3$) δ 16.38 and 17.16 (q, Me C-3), 28.04 and 28.28 (q, C-1), 32.31 (t, C-4), 42.67 and 43.80 (d, C-3), 63.41 and 64.1 (t, C-6), 78.56 and 78.82 (d, Py C-2), 126.23 and 126.43 (d, Py C-4), 147.88 (d, C-5), 195.74 (s, Py C-3), 211.91 (s, C-2). Anal. Calcd for $C_{10}H_{14}O_3 \cdot 0.5H_2O$: C, 62.80; H, 7.90. Found: C, 62.50; H, 7.57.

(*R*)-1,1-Bis(acetyloxy)-3,6-dihydro-α,α-dimethyl-3-oxo-2*H*-pyran-2-propanal (7b): 14% (hexane–ethyl acetate–dichloromethane (27.5:22.5:50)); $[\alpha]^{20}_D$ = +15° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02 and 1.04 (two s, 6 H, Me C-2), 1.65 (dd, 1 H, *J* = 9.69 and 15.1 Hz, H-3), 2.09 and 2.10 (two s, 6 H, CH_3CO), 2.17 (dd, 1 H, *J* = 1.98 and 15.1 Hz, H-3), 4.13 (dd, 1 H, *J* = 1.98 and 9.69 Hz, Py H-2), 4.38 (m, 2 H, H-6), 6.17 (ddd, 1 H, *J* = 2.07, 2.07 and 10.33 Hz, H-4), 6.73 (s, 1 H, H-1), 7.05 (ddd, 1 H, *J* = 2.76, 2.76, and 10.33 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 20.73 (q, CH_3CO), 21.88 and 22.41 (q, Me C-2), 35.83 and 36.90 (t, C-3), 63.93 (t, C-6), 78.19 (d, Py C-2), 93.03 (d, C-1), 126.14 (d, C-4), 147.88 (d, C-5), 169.02 (s, CH_3CO), 195.78 (s, Py C-3). Anal. Calcd for $C_{14}H_{20}O_6 \cdot 0.5H_2O$: C, 57.32; H, 7.21. Found: C, 57.08; H, 6.85.

[*S*-[*S,*R**,*S**]]-3-Methyl-4-[3,6-dihydro-3-oxo-2*H*-pyran-2-yl]-2-butanone (9a)**. 70% (hexane–ethyl acetate (5:5)); $[\alpha]^{20}_D$ = −37.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (d, 2.1 H, *J* = 7.01 Hz, Me C-3 (*S*)), 1.15 (d, 0.9 H, *J* = 7.12 Hz, Me C-3 (*R*)), 1.77 (ddd, 0.3 H, *J* = 4.25, 8.32, and 14.55 Hz, H-4 (*R*)), 1.91 (ddd, 0.7 H, *J* = 3.65, 6.9, and 14.63 Hz, H-4 (*S*)), 2.1 (ddd, 0.7 H, *J* = 7.3, 9.75, and 14.63 Hz, H-4 (*S*)), 2.19 (s, 3 H, H-1), 2.37 (ddd, 0.3 H, *J* = 4.15, 9.22, and 14.55 Hz, H-4 (*R*)), 2.75 (m, 1 H, H-3), 4 (m, 1 H, Py H-2), 4.25–4.33 (m, 2 H, H-6), 6.15 (dd, 1 H, *J* = 2.19 and 10.36 Hz, Py H-4), 7.05 (dd, 1 H, *J* = 2.66 and 10.36 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 16.8 and 17.5 (q, Me C-3), 28 and 28.2 (q, C-1), 32.4 and 32.6 (t, C-4), 42.4 and 44 (d, C-3), 63.4 and 64 (t, C-6), 78.6 and 78.9 (d, Py C-2), 126 and 126.2 (d, Py C-4), 147.8 and 148 (d, C-5), 196 (s, Py C-3), 212 (s, C-2). Anal. Calcd for $C_{10}H_{14}O_3 \cdot 0.5H_2O$: C, 62.80; H, 7.90. Found: C, 62.94; H, 7.66.

(*S*)-1,1-Bis(acetyloxy)-3,6-dihydro-α,α-dimethyl-3-oxo-2*H*-pyran-2-propanal (9b): 10% (hexane–ethyl acetate (5:5)); $[\alpha]^{20}_D$ = −17.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H, *J* = 7 Hz, Me C-2), 1.13 (s, 3 H, *J* = 7 Hz, Me C-2), 1.65 (dd, 1 H, *J* = 9.7 and 15.1 Hz, H-3), 2.09 and 2.10 (s, 6 H, CH_3CO), 2.17 (dd, 1 H, *J* = 1.89 and 15.1 Hz, H-3), 4.15 (dd, 1 H, *J* = 1.98 and 9.7 Hz, Py H-2), 4.4 (m, 2 H, H-6), 6.15 (ddd, 1 H, *J* = 2.07, 2.07, and 10.33 Hz, H-4), 6.73 (s, 1 H, H-1), 7.1 (ddd, 1 H, *J* = 2.76, 2.76 and 10.33 Hz, H-5); ^{13}C RMN ($CDCl_3$) δ 20.76 (q, CH_3CO), 21.92 and 22.43 (q, Me C-2), 35.83 and 35.88 (t, C-3), 63.65 (t, C-6), 78.27 (d, Py C-2), 93.04 (d, C-1), 126.52 (d, C-4), 147.70 (d, C-5), 169.14 (s, CH_3CO), 195.87 (s, Py C-3). Anal. Calcd for $C_{14}H_{20}O_6 \cdot H_2O$: C, 55.62; H, 7.34. Found: C, 55.42; H, 7.15.

[2*S*-[2α(*R,*S**),6β]]-1,1-Bis(acetyloxy)-3,6-dihydro-α,6-dimethyl-3-oxo-2*H*-pyran-2-propanal (11)**: 60% (hexane–ethyl acetate (1:1)); $[\alpha]^{20}_D$ = +25° (*c* 0.1, $CHCl_3$); ^1H NMR (300.13 $CDCl_3$) δ 1.05 (d, 2.25 H, *J* = 7.02 Hz, Me C-2 (*S*)), 1.07 (d, 0.75 H, *J* = 6.94 Hz, Me C-2 (*R*)), 1.4 (d, 2.25 H, *J* = 6.64 Hz Hz, Me C-6 (*S*)), 1.42 (d, 0.75 H, *J* = 6.78 Hz, Me C-6 (*S*)), 1.55 (ddd, 0.75 H, *J* = 3.34, 10.41, and 14.3 Hz, H-3 (*S*)), 1.68 (ddd, 0.25 H, *J* = 6.2, 9.06, and 14.3 Hz, H-3 (*R*)), 1.95 (ddd, 0.25 H, *J* = 3.81, 11.44, and 14.3 Hz, H-3 (*R*)), 2.08 (m, 0.75 H, H-3 (*S*)), 2.1 (s, 6 H, CH_3CO), 2.2 (m, 1 H, H-2), 4.25 (dd, 0.75 H, *J* = 3.34 and 11.44 Hz, Py H-2 (*S*)), 4.35 (dd, 0.25 H, *J* = 4.77 and 9.06 Hz, Py H-2 (*R*)), 4.55 (m, 1 H, H-6), 6.02 (dd, 0.25 H, *J* = 2.07 and 10.49 Hz, H-4 (*R*)), 6.04 (dd, 0.75 H, *J* = 2.18 and 10.49 Hz, H-4 (*S*)), 6.76 (d, 0.75 H, *J* = 3.34 Hz, H-1 (*S*)), 6.77 (d, 0.25 H, *J* = 3.34 Hz, H-1 (*R*)), 6.95 (dd, 1 H, *J* = 2.86 and 10.49 Hz, H-5). Anal. Calcd for $C_{14}H_{20}O_6 \cdot 0.5H_2O$: C, 57.32; H, 7.21. Found: C, 57.50; H, 6.81.

[*R*-[*R,*R**,*S**]]-1,1-Bis(acetyloxy)-3,6-dihydro-α-methyl-3-oxo-2*H*-pyran-2-propanal (13)**: 70% (hexane–ethyl acetate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = +21.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.04 (d, 1.5 H, *J* = 6.8 Hz, Me C-2 (*R*)), 1.06 (s, 1.5 H, *J* = 6.80 Hz, Me C-2 (*R*)), 1.6 (ddd, 0.5 H, *J* = 5.25, 8.5 and 14.3 Hz, H-3 (*R*)), 1.87 (m, 1 H, H-3 (*S*)), 2.15 (two s, 6 H, CH_3CO), 2.18 (ddd, 0.5 H, *J* = 3.8, 8.2 and 14.3 Hz, H-3 (*R*)), 2.25 (m, 1 H, H-2), 4.05 (m, 0.5 H, Py H-2 (*R*)), 4.3 (m, 0.5 H, Py H-2 (*S*)), 4.45 (m, 2 H, H-6), 6.17 (ddd, 1 H, *J* = 2.86, 3.8, and 10.49, H-4), 6.75 (d, 0.5 H, *J* = 3.77 Hz, H-1 (*R*)), 6.8 (d, 0.5 H, *J* = 3.48 Hz, H-1 (*S*)), 7.06 (ddd, 1 H, *J* = 2.38, 3.34, and 10.49 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 13.00 and 14.55 (q, Me C-2), 20.84 (q, CH_3CO), 30.03 and 30.80 (t, C-2), 32.79 and 33.02 (d, C-3), 63.82 and 64.19 (t, C-6), 78.07 and 78.90 (d, Py C-2), 91.60 and 92.22 (d, C-1), 126.55 (d, C-4), 147.91 (d, C-5), 169.09 (s, CH_3CO), 196.07 (s, Py C-3). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.69; H, 6.21.

[*S*-[*S,*R**,*S**]]-1,1-Bis(acetyloxy)-3,6-dihydro-α-methyl-3-oxo-2*H*-pyran-2-propanal (14)**: 70% (hexane–ethyl acetate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = −19° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.04 (d, 1.5 H, *J* = 6.8 Hz, Me C-2 (*S*)), 1.06 (d, 1.5 H, *J* = 6.8 Hz, Me C-2 (*R*)), 1.6 (ddd, 0.5 H, *J* = 5.25, 8.6 and 14.3 Hz, H-3 (*S*)), 1.87 (m, 1 H, H-3 (*R*)), 2.15 (two s, 6 H, CH_3CO), 2.18 (ddd, 0.5 H, *J* = 3.8, 8.2, and 14.3 Hz, H-3 (*S*)), 2.25 (m, 1 H, H-2), 4.05 (m, 0.5 H, Py H-2 (*R*)), 4.3 (m, 0.5 H, Py H-2 (*S*)), 4.45 (m, 2 H, H-6), 6.17 (ddd, 1 H, *J* = 2.86, 3.08, and 10.49, H-4), 6.75 (d, 0.6 H, *J* = 3.77 Hz, H-1 (*S*)), 6.8 (d, 0.5 H, *J* = 3.46 Hz, H-1 (*R*)), 7.05 (ddd, 1 H, *J* = 2.38, 3.34, and 10.49 Hz, H-5). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.15; H, 6.31.

[2*S*-[2α(*R,*S**),6β]]-3,6-Dihydro-α,6-dimethyl-3-oxo-2*H*-pyran-2-propanal (15)**: 53% (hexane–ethyl acetate (1:1)); $[\alpha]^{20}_D$ = +25° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (d, 3 H, *J* = 7.05 Hz, Me C-2), 1.37 (d, 1.5 H, *J* = 6.96 Hz, Me C-6 (*S*)), 1.38 (d, 1.5 H, *J* = 6.94 Hz, Me C-6 (*R*)), 1.75 (ddd, 0.5 H, *J* = 3.33, 7.63, and 14.59 Hz, H-3 (*S*)), 1.95 (ddd, 0.5 H, *J* = 4.76, 9.06, and 14.59 Hz, H-3 (*R*)), 2.15–2.3 (m, 1 H, H-3 (*R*) and H-3 (*S*)), 2.6 (m, 1 H, H-2), 4.25 (dd, 0.5 H, *J* = 3.33 and 10.70 Hz, Py H-2 (*S*)), 4.27 (dd, 0.5, H, *J* = 4.35 and 9.06 Hz, Py H-2 (*R*)), 4.55 (m, 1 H, H-6), 6.03 (dd, 0.5 H, *J* = 1.95 and 10.42 Hz, H-4 (*S*)), 6.04 (dd, 0.5 H, *J* = 2.03 and 10.42 Hz, H-4 (*R*)), 6.97 (dd, 1 H, *J* = 2.86 and 10.42 Hz, H-5), 9.63 (d, 0.5 H, *J* = 1.9 Hz, H-1), 9.68 (d, 0.5 H, *J* = 1.9

Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 13.40 (q, Me C-2), 18.37 and 20.76 (q, Me C-6), 30.15 and 30.33 (t, C-3), 42.35 and 43.28 (d, C-2), 65.94 (d, C-6), 74.78 (d, Py C-2), 124.77 (d, C-4), 151.66 and 151.81 (d, C-5), 195.80 (s, Py C-3), 203.90 (s, C-1).

[*R*-[*R,*R***S**]]-3,6-Dihydro-α-methyl-3-oxo-2*H*-pyran-2-propanal (16)**: 66.5% (hexane–ethyl acetate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = +14° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, 1.5 H, *J* = 7.07 Hz, Me C-2), 1.18 (d, 1.5 H, *J* = 7.14 Hz, Me C-2), 1.9 (ddd, 0.5 H, *J* = 3.79, 8.72 and 14.41 Hz, H-3 (*R*)), 2–2.2 (m, 1 H, H-3 (*S*)), 2.4 (ddd, 0.5 H, *J* = 3.79, 8.72, and 14.41 Hz, H-3 (*R*)), 2.6 (m, 1 H, H-2), 4.1 (m, 1 H, Py H-2), 4.4 (m, 2 H, H-6), 6.15 (dd, 1 H, *J* = 1.98, 2.09, and 10.24 Hz, H-4), 7.1 (dd, 1 H, *J* = 2.21, 2.92, and 10.24 Hz, H-5), 9.62 (d, 0.5 H, *J* = 2.21 Hz, H-1), 9.64 (0.5 H, *J* = 1.9 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 13.73 and 20.97 (q, Me C-2), 30.61 (t, C-3), 42.44 and 43.01 (d, C-2), 63.90 and 64.23 (t, C-6), 78.15 and 78.61 (d, Py C-2), 126.49 (d, C-4), 148 (d, C-5), 195.90 (s, Py C-3), 204.42 (d, C-1).

[*S*-[*S,*R***S**]]-3,6-Dihydro-α-methyl-3-oxo-2*H*-pyran-2-propanal (17)**: 70% (hexane–ethyl acetate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = −10 (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.17 (d, 0.5 H, *J* = 7.06 Hz, Me C-2), 1.18 d, 0.5 H, *J* = 7.12 Hz, Me C-2), 1.9 (ddd, 0.5 H, *J* = 3.7, 8.51, and 14.80 Hz, H-3 (*S*)), 2–2.2 (m, 1 H, H-3 (*R*)), 2.4 (ddd, 0.5 H, *J* = 3.7, 8.51, and 14.80 Hz, H-3 (*S*)), 2.6 (m, 1 H, H-2), 4.1 (m, 1 H, Py H-2), 4.4 (m, 2 H, H-6), 6.15 (dd, 1 H, *J* = 1.85, 2.2, and 10.36 Hz, H-4), 7.1 (dd, 1 H, *J* = 1.87, 2.62, and 10.36 Hz, H-5), 9.62 (d, 0.5 H, *J* = 2.29 Hz, H-1), 9.64 (0.5 H, *J* = 1.87 Hz, H-1); ^{13}C NMR δ 13.70 and 20.94 (q, Me C-2), 30.59 (t, C-3), 42.42 and 43.37 (d, C-2), 63.98 and 64.20 (t, C-6), 78.15 and 78.59 (d, Py C-2), 126.44 (d, C-4), 147.98 (d, C-5), 195.59 (s, Py C-3), 204.28 (d, C-1).

[*R*-[*R,*R***S**]]-1,1-Bis(acetyloxy)-1,2-dideuterio-3,6-dihydro-α-methyl-3-oxo-2*H*-pyran-2-propanal (23)**: 70% (hexane–ethyl acetate–dichloromethane (3:2:5)); $[\alpha]^{20}_D$ = +45° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (s, 1.62 H, Me C-2 (*R*)), 1.02 (s, 1.38 H, Me C-2 (*S*)), 1.6 (dd, 0.54 H, *J* = 8.85 and 14.8 Hz, H-3(*R*)), 1.87 (m, 0.92 H, H-3 (*S*)), 2.15 (two s, 6 H, CH_3CO), 2.18 (ddd, 0.54 H, *J* = 4.29 and 14.8 Hz, H-3 (*R*)), 4.05 (m, 0.54 H, Py H-2 (*R*)), 4.3 (m, 0.46 H, Py H-2 (*S*)), 4.45 (m, 2 H, H-6), 6.17 (ddd, 1 H, *J* = 2.86, 3.8, and 10.49 Hz, H-4), 7.1 (ddd, 1 H, *J* = 2.81, 3.81, and 10.49 Hz, H-5).

[2*S*-[2α(*R*S**),5α,6β]]-5-(Acetyloxy)-α,6-dimethyl-5,6-dihydro-2*H*-pyran-2-propanal (25)**: $[\alpha]^{20}_D$ = −77° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (s, 2 H, Me C-2 (*S*)), 1.16 (s, 1 H, Me C-2 (*R*)), 1.21 (d, 1 H, *J* = 6.7 Hz, Me C-6 (*R*)), 1.38 (d, 2 H, *J* = 6.7 Hz, Me C-6 (*S*)), 1.42 (dd, 0.66 H, *J* = 3.64 and 14.58 Hz, H-3 (*S*)), 1.78 (dd, 0.33 H, *J* = 9.11 and 14.58 Hz, H-3 (*R*)), 1.94 (dd, 0.33 H, *J* = 3.95 and 14.58 Hz, H-3 (*R*)), 2.1 (s, 3 H, CH_3CO), 2.15 (dd, 0.66 H, *J* = 10.32 and 14.58 Hz, H-3 (*S*)), 3.85 (dq, 1 H, *J* = 5.6 and 7 Hz, H-6), 4.25 (m, 1 H, Py H-2), 4.86 (m, 1 H, H-5), 5.74–5.92 (m, 2 H, Py H-3 and H-4).

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Ircinals A and B from the Okinawan Marine Sponge *Ircinia* sp.: Plausible Biogenetic Precursors of Manzamine Alkaloids

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The manzamines, which have been isolated from marine sponges,[2-4] comprise a new group of β-carboline alkaloids having intricate polycyclic systems. The provenance of the nitrogen-containing ring systems embraced in the manzamine alkaloids has been problematical since there appears to be no obvious biogenetic path. During our studies on bioactive substances from Okinawan marine organisms,[5] we have isolated two novel alkaloids, ircinals A (1) and B (2), which might be plausible biogenetic precursors of the manzamine alkaloids, from the Okinawan marine sponge *Ircinia* sp. Here, we describe the isolation and structure elucidation of 1 and 2 as well as two new manzamine congeners, manzamines H (3) and J (4), from the same sponge. Ircinals A (1) and B (2) were converted into manzamines A (5) and J (4), respectively, through Pictet–Spengler cyclization with tryptamine followed by DDQ oxidation. Ircinals A (1) and B (2) and manzamines H (3) and J (4) exhibited cytotoxicity.

The sponge *Ircinia* sp. was collected off Kise, Okinawa, and kept frozen until processing. The methanol extract of the sponge was partitioned between ethyl acetate and water. The ethyl acetate soluble material was subjected

Table I. ^1H and ^{13}C NMR Chemical Shifts (ppm) of Ircinal A (1) and Protons to which Long-Range Correlations Were Observed in the HMBC Experiments

position	^{13}C	^1H	*J* (Hz)	HMBC (^1H)
1	193.3 d	9.45 s		H-11, H-24
10	142.6 s			H-1, H-23, H-24
11	157.6 d	6.75 s		H-13, H-24, H-26
12	70.2 s			H-13, H-26
13	38.9 t	1.61 m, 1.77 m		H-14, H-26
14	21.0 t	2.11 m, 2.24 m		H-15, H-16
15	127.9 d	5.56 m		H_2-14
16	132.5 d	5.50 dddd	10.7, 10.7, 10.7, 4.6	H-14
17	25.6 t	1.63 m, 2.43 m		H-15, H-16
18	26.7 t	1.25 m, 1.41 m		H-20
19	25.3 t	1.38 m, 1.71 m		H_2-20
20	53.5 t	2.39 m, 2.57 m		H-36
22	49.4 t	1.86 m, 2.77 m		H-20, H-23, H_2-36
23	31.6 t	1.22 m, 1.78 m		H-24
24	34.0 d	2.58 dd	12.2, 6.8	H-11, H-22, H-23, H-35, H-36
25	46.4 s			H-24, H-26, H-34, H-35, H-36
26	76.3 d	3.44 s		H-11, H-13, H-24, H-34, H-35, H_2-36
28	51.4 t	3.04 m, 3.38 m		H-26
29	29.8 t	1.73 m, 1.93 m		H-28, H-31
30	25.3 t	1.35 m, 1.89 m		H_2-28, H_2-31, H-32
31	28.2 t	2.14 m, 2.29 m		H-32, H-33
32	137.1 d	6.03 dddd	11.0, 7.1, 7.1, 1.5	H-30, H_2-31, H-33, H-34
33	127.7 d	5.26 ddd	10.5, 10.3, 1.2	H-34, H_2-35
34	55.4 d	4.36 br t	8.1	H-28, H-32, H-33, H-35
35	44.6 t	1.67 m, 1.86 m		H-24, H-26, H-33, H-34, H_2-36
36	69.2 t	2.29 d, 2.81 d	11.2	H-22, H-26, H_2-35

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