Stereoselectivity Reversals in Conjugate Additions to a 2,3-Dihydro-4*H*-pyran-4-one†

Thomas E. Goodwin,* N. Michele Rothman, Karen L. Salazar, and Shannon L. Sorrels

Department of Chemistry, Hendrix College, Conway, Arkansas 72032-3080

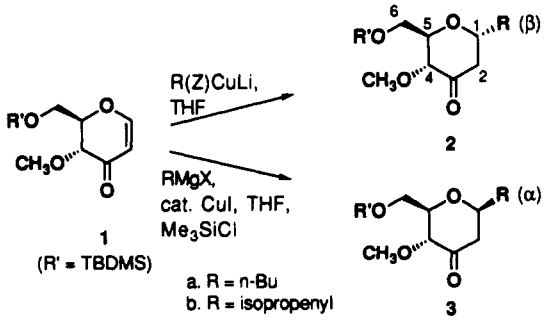
Frederick E. Evans

Division of Biochemical Toxicology, National Center for Toxicological Research, Jefferson, Arkansas 72079

Received August 2, 1991

Recently, there has been increasing interest in the class of simple heterocycles known as 2,3-dihydro-4*H*-pyran-4-ones (**1**).[1] This interest stems in part from three areas: (1) the discovery of natural products possessing this ring system (for example, hepialone, a sex pheromonal component of the ghost moth[2]); (2) improved methods of preparation, exemplary among which is the hetero Diels–Alder methodology of the Danishefsky group;[3,4] and (3) the usefulness of these enones as intermediates in the synthesis of natural products, such as forskolin[5] and milbemycin β_3.[6] The first example of conjugate addition of an organometallic reagent to one of these heterocyclic enones was reported by Fraser-Reid and his co-workers[7] and was essentially nonstereoselective. Subsequently, several other accounts of successful conjugate additions have been recorded,[5,6,8] most of which involve bicyclic enones where conformational restrictions and severe steric interactions provide a clear rationale for any observed stereoselectivities.

Several years ago a report from these laboratories described some stereoselective additions of organocopper reagents to a conformationally mobile, monocyclic, carbohydrate-derived enone (**1** to **2**)[9] in yields ranging from 64 to 94%. In all cases the major product was that in which the new alkyl group and the methoxy were cis (hereafter referred to as β).[10] More recent results have revealed that copper(I)-catalyzed Grignard addition to enone **1** yields adducts of opposite C-1 stereochemistry as the major reaction products **3** (hereafter referred to as α).[10] Stereoselectivity reversals of this sort in conjugate additions to pyranyl enones are not without precedent. In copper(I)-catalyzed conjugate additions to a spirocyclic enone, Crimmins and his co-workers[6] observed that the stereochemistry of addition could be reversed upon variation of the solvent and/or the copper catalyst.[11] In this paper a discussion of recent results from these laboratories is followed by reasonable rationalizations of the stereochemical observations.



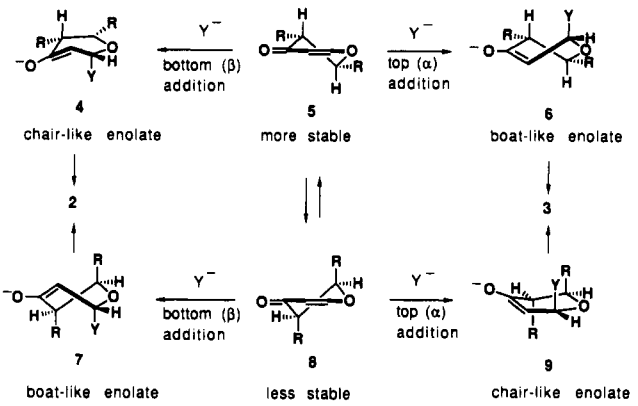
For comparative purposes, four reactions were carried out in this preliminary investigation. Stoichiometric organocopper additions provided predominantly compound **2a** (prepared via a homocuprate or mixed heterocuprate reagent as described previously[9]) and compound **2b** (prepared via the procedure of Lipshutz et al.,[8d,12] which was

Table I. Yields and Isomer Ratios[a] for Conjugate Additions

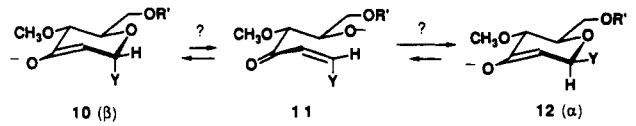
reaction	% yield[b]	3:2 ratio[a]
R(Z)CuLi; *n*-Bu series	94	1:12.9
R(Z)CuLi; isopropenyl series	80	1:3.2
RMgX, CuI; *n*-Bu series[c]	79	6.9:1
RMgX, CuI; isopropenyl series[c]	63	2.9:1

[a] Ratios determined by integration of the respective methoxy singlets in the 500-MHz ^{1}H NMR spectra. [b] After purification. [c] Data are reported for Grignard reactions in which Me_3SiCl was present. A similar 3:2 ratio was observed in the absence of Me_3SiCl, although in slightly lower yield.

Scheme I



Scheme II



(1) Often these heterocycles (**1**) are known in the carbohydrate literature as "hex-1-enopyran-3-uloses".

(2) (a) Kubo, I.; Matsumoto, T.; Wagner, D. L. *Tetrahedron Lett.* **1985**, *26*, 563. (b) Uchino, K.; Yamagiwa, Y.; Kamikawa, T.; Kubo, I. *Ibid.* **1985**, *26*, 1319. (c) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585. (d) For a related pheromone, see: Deschenaux, P.-F.; Kallimopoulos, T.; Jacot-Guillarmod, A. *Helv. Chim. Acta* **1989**, *72*, 1259.

(3) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636 and references contained therein.

(4) For a recent synthesis from acetylenic ketones, see the following: Obrecht, D. *Helv. Chim. Acta* **1991**, *74*, 27.

(5) Ziegler, F. E.; Jaynes, B. H. *Tetrahedron Lett.* **1988**, *29*, 2031 and references contained therein.

(6) Crimmins, M. T.; Bankaitis-Davis, D. M.; Hollis, W. G. *J. Org. Chem.* **1988**, *53*, 652.

(7) Yunker, M. B.; Plaumann, D. E.; Fraser-Reid, B. *Can. J. Chem.* **1977**, *55*, 4002.

(8) Inter alia: (a) Wratten, S. J.; Meinwald *Tetrahedron Lett.* **1980**, *21*, 3163. (b) Sakai T.; Miyata, K.; Ishikawa, M.; Takeda, T. *Ibid.* **1985**, *26*, 4727. (c) Delpech, B.; Lett, R. *Ibid.* **1987**, *28*, 4061. (d) Boring, D. L.; Sindelar, R. D. *J. Org. Chem.* **1988**, *53*, 3617.

(9) Goodwin, T. E.; Crowder, C. M.; White, R. B.; Swanson, J. S.; Evans, F. E.; Meyer, W. L. *J. Org. Chem.* **1983**, *48*, 376.

(10) (a) The carbohydrate numbering hierarchy which is depicted on structure **2** is used throughout this paper, the sole exception being in the current *Chemical Abstracts* nomenclature which is used for compound names in the Experimental Section. (b) In traditional carbohydrate parlance, a substituent at C-1 would be designated α or β by analogy to the usual anomeric center. In the present case, however, current *Chemical Abstracts* rules result in a reversal of the carbohydrate designations; for example, the alkyl group at C-1 in structure **2** is designated β due to its trans relationship to the substituent at C-5. These latter designations for α and β are used exclusively in this paper.

(11) Reagent- and solvent-dependent stereoselectivity in organocopper addition to some carbocyclic enones has been observed; e.g., see: Zhao, S.-K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447 and references cited therein.

† Dedicated to Professor Ernest Wenkert on the occasion of his 66th birthday.

0022-3263/92/1957-2469$03.00/0

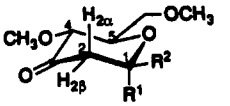
in this case far superior to the mixed heterocuprate reagents employed previously[9]). The isomeric adducts (**3a** and **3b**) were predominant in copper(I)-catalyzed Grignard additions using a modification[13] of the procedure of House.[14] Overall yields and isomer ratios of purified product mixtures are listed in Table I.

One explanation for these results involves the stereoelectronic effects first proposed by Toromanoff[15] with later elaboration by Deslongchamps.[16] Normally, kinetically-controlled conjugate additions to conjugated enones take place preferentially by way of the chair-like enolate which results from the more stable half-chair conformer. In Scheme I this route involves half-chair **5** and enolate **4** and would produce the β adducts **2**. The α adducts **3** could arise in either of two ways: kinetic addition to the more stable half-chair **5** to provide the boat-like enolate **6**, or kinetic addition to the less stable half-chair **8** to provide the chair-like enolate **9** (an unlikely prospect since this pathway is not only disfavored by the presumed instability of **8**, but also by the destabilizing influence of one axial and two pseudoaxial substituents in the transition state leading to enolate **9**). This logic would suggest, then, that the stoichiometric organocopper reagents react preferentially through enolate **4**, while the copper-catalyzed Grignard additions occur predominantly via enolate **6**.

A simple, yet compelling explanation postulates an identical mode of kinetic addition for both the stoichiometric and catalytic cuprate reactions (i.e. **5** to **4**, Scheme I), followed in the catalytic reactions alone by a "favored" 6-*endo-trig* ring opening[17] (Scheme II, **10** to **11**); the putative equilibrium thus established would be expected to favor the all equatorial isomer **12** (i.e. the α adduct).[18]

Further investigations will be required to determine which (if either) of the foregoing stereochemical explanations is correct, as well as to ascertain the reaction conditions which will optimize production of either the α or the β adduct.[19] Nonetheless, the ability to create a new chiral center on a tetrahydropyranyl ring in either absolute configuration by choice of the proper organometallic reagent and reaction conditions bodes well for the use of these conjugate additions in natural products synthesis.

Throughout this work, tetrahydropyranone rings have been assumed to be in a chair conformation in which the C-4 and C-5 substituents are equatorial, an assumption which has previously been used successfully.[9] Of interest in this regard are molecular modeling results on model systems **13** and **14**. MM2 calculations[20] led to the following predicted coupling constants: for **13**, $J_{1,2\alpha}$ = 5.7 Hz, $J_{1,2\beta}$ = 1.2 Hz, and $J_{4,5}$ = 9.3 Hz (the corresponding experimental values (averaged for **2a** and **2b**) are 6.2, 3.5, and 8.6 Hz, respectively); for **14**, $J_{1,2\alpha}$ = 11.7 Hz, $J_{1,2\beta}$ = 2.7 Hz, and $J_{4,5}$ = 9.5 Hz (the corresponding experimental data (averaged for **3a** and **3b**) are 11.7, 2.3, and 9.6 Hz, respectively). Clearly, calculations of this sort can be used with some confidence for conformational analysis and prediction of NMR coupling constants for these heterocycles.



13; R^1 = CH_3; R^2 = H
14; R^1 = H; R^2 = CH_3

Experimental Section

General Methods. THF was distilled from $LiAlH_4$ immediately before use. Solutions of $NaHCO_3$, NaOAc, and NaCl (brine) were aqueous and saturated. Solutions of unpurified reaction products were dried over anhydrous Na_2SO_4. ^1H NMR spectral assignments were aided by computer simulations of the spectra.

[2*R*-(2α,3β,6β)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-4*H*-pyran-4-one (2a). The method of preparation for this compound has been published.[9] It was isolated as a 1:12.9 mixture of α:β isomers. Physical constants for the α isomer (**3a**) are reported separately below, while those for the β isomer (**2a**) have been reported,[9] except for the following: ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.4 and −5.5 ($Si(Me)_2$), 13.9 (Me of *n*-Bu), 18.3 (quaternary C of *t*-Bu), 22.3 (C-3′, CH_2 of *n*-Bu), 25.8 (3 Me of *t*-Bu), 27.4 (C-2′, CH_2 of *n*-Bu), 32.2 (C-1′, CH_2 of *n*-Bu), 45.8 (CH_2 of ring), 59.0 (OMe), 63.2 (C-6), 74.1 (C-1), 76.3 (C-5), 81.5 (C-4), 206.8 (C=O).

[2*R*-(2α,3β,6β)]-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-6-(1-methylethenyl)-4*H*-pyran-4-one (2b). This preparation follows the general procedure of Lipshutz, Wilhelm, and Kozlowski.[12] *n*-Butyllithium (0.84 mL of a 2.5 M solution in hexanes; 2.1 mmol) was added to a stirred of 2-bromopropene (253 mg, 2.093 mmol) in 1.5 mL of THF under Ar at −78 °C. Stirring at this temperature was continued for 1.5 h, at which time the cold solution was transferred under Ar pressure by double-tipped needle to a flask containing a stirred suspension of CuCN (94 mg, 1.050 mmol) in 3 mL of THF which was also at −78 °C. The reaction flask was then removed from the cooling bath, allowed to warm to −20 °C with stirring under Ar (at which time virtually all of the suspended CuCN was in solution), and then recooled to −78 °C. A solution of enone **1**[9] (190 mg, 0.699 mmol) in 2 mL of THF was added, and stirring at −78 °C was continued for 3 h. One milliliter of an aqueous mixture of NaOH and NH_4Cl (1:9 v/v 10% NaOH/saturated NH_4Cl) was added, the flask was removed from the cooling bath, and stirring under Ar was continued for 0.5 h. The reaction mixture was diluted with ether (150 mL), filtered over Celite, washed with brine, and dried. Removal of solvent in vacuo provided the crude product. Purification was effected by flash chromatography[21] (silica gel; 3:1 petroleum ether/ether) to provide the adduct (175 mg, 80%), a pale yellow liquid, as a 1:3.2 mixture of α:β isomers. Physical constants for the α isomer (**3b**) are reported separately below, while those for the β isomer (**2b**) are as follows: IR ($CHCl_3$) 3090 (w), 1724 (s), 1645 (w), 1459 (m), 1252 (m), 1124 (s), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.07, 0.08 (both s, 3 H each, $SiMe_2$), 0.90 (s, 9 H, *t*-Bu), 1.73 (br s, 3 H, Me of isopropenyl), 2.76 (ddd, 1 H, J_{gem} = 14.6 Hz, $J_{1,2\alpha}$ = 6.3 Hz, $J_{2\alpha,4}$ = 1.0 Hz, H-2α), 2.81 (dd, 1 H, $J_{1,2\beta}$ = 3.1 Hz, H-2β), 3.47 (s, 3 H, OMe), 3.56 (dt, 1 H, $J_{4,5}$ = 8.9 Hz, $J_{5,6}$ = 3.0 Hz, H-5), 3.77 (dd, 1 H, H-4), 3.82 (d, 2 H, H-6), 4.63 (m, 1 H, H-1), 4.93 (br s, 1 H, vinyl H), 5.03 (br s, 1 H, vinyl H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.5 (both $Si(Me)_2$), 18.3 (quaternary C of *t*-Bu), 19.9

(12) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.
(13) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.
(14) House, H. O.; Latham, R. A.; Slater, C. D. *J. Org. Chem.* **1966**, *31*, 2667.
(15) Toromanoff, E. *Bull. Soc. Chim. Fr.* **1962**, 708.
(16) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 6 and references cited therein.
(17) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.
(18) A similar ring opening has been observed for thian-4-ones; cf.: (a) Batten, R. J.; Coyle, J. D.; Taylor, R. G. K. *Synthesis* **1980**, 910. (b) Batten, R. J.; Coyle, J. D.; Taylor, R. J. K.; Vassiliou, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1177.
(19) (a) For interesting mechanistic speculations involving variable stereoselectivity in organocopper additions to a carbocyclic enone, see: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) For useful comments on the possible roles of Me_3SiCl in organocopper conjugate additons, see: Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087.
(20) MM2 calculations were carried out using MODEL (version K.S. 2.96). Global minimizations were performed using BAKMDL, MODEL's batch mode minimizer. MODEL's ^1H NMR calculation is based on a modified Karplus algorithm of Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(vinyl Me), 25.9 (3 Me of t-Bu), 43.1 (CH_2 of ring), 59.4 (OMe), 63.0 (C-6), 76.0 (C-1 and C-5), 81.5 (C-4), 115.9 (vinyl CH_2), 142.5 (quaternary vinyl C), 206.6 (C=O); MS *m/e* 314, 257, 225, 197, 173, 161, 132, 117, 98, 89 (base); exact mass for $C_{16}H_{30}O_4Si$ calcd 314.1913, found 314.1908.

[2*R*-(2α,3β,6α)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-4*H*-pyran-4-one (3a). This compound was prepared basically as described below for compound **3b** in 79% yield as a pale yellow liquid which was isolated as a 6.9:1 mixture of α:β isomers. Physical constants for the β isomer (**2a**) are reported separately[9] (^{13}C NMR data are listed above), while those for the α isomer (**3a**) are as follows: IR ($CHCl_3$) 1722 (s), 1460 (m), 1252 (m), 1016 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08, 0.09 (both s, 3 H each, $SiMe_2$), 0.89 (t, 3 H, J = 10.1 Hz, Me of n-Bu), 0.91 (s, 9 H, *t*-Bu), 1.22–1.66 (m, 6 H, $(CH_2)_3$), 2.34 (dd, 1 H, J_{gem} = 13.5 Hz, $J_{1,2\beta}$ = 2.3 Hz, H-2β), 2.44 (ddd, 1 H, $J_{1,2\alpha}$ = 11.4 Hz, $J_{2\alpha,4}$ = 1.2 Hz, H-2α), 3.39 (ddd, 1 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 3.5 Hz, $J_{5,6b}$ = 1.8 Hz, H-5), 3.50 (s, 3 H, OMe), 3.52–3.58 (m, 1 H, H-1), 3.83–3.90 (m, 3 H, H-4, H-6a, H-6b); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.1 and −5.3 ($Si(Me)_2$), 13.9 (Me of *n*-Bu), 18.3 (quaternary C of *t*-Bu), 22.4 (C-3′ CH_2 of *n*-Bu), 25.8 (3 Me of t-Bu), 27.4 (C-2′, CH_2 of *n*-Bu), 35.6 (C-1′, CH_2 of *n*-Bu), 48.0 (CH_2 of ring), 59.6 (OMe), 62.7 (C-6), 77.6 (C-5), 81.5 (C-1), 81.8 (C-4), 207.1 (C=O); MS *m/e* 307, 273, 241, 185, 161, 131 (base), 117, 89; exact mass for $C_{17}H_{34}O_4Si$ calcd 330.2226, found 330.2214.

[2*R*-(2α,3β,6α)]-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-6-(1-methylethenyl)-4*H*-pyran-4-one (3b). This procedure was adapted from one by House, Latham, and Slater[14] with modifications suggested by the work of Nakamura and Kuwajima et al.[13] Magnesium turnings (956 mg, 39.3 mmol) were broken into small pieces, placed in a dry 500-mL flask, rinsed three times with THF, and covered with THF (12 mL). A small iodine crystal was added, and the flask was flushed with N_2. In a test tube were placed Mg turnings (approximately 100 mg), a few drops of 2-bromopropene, and THF (1 mL). The test tube reaction was initiated by gently breaking some of the turnings with a stirring rod, and then 5–10 drops of the solution were added via syringe to the reaction flask. The mixture was stirred under N_2 without external heating or cooling as a mixture of 2-bromopropene (6.59 g, 0.0545 mol) and THF (3.5 mL) was added over 1 h. The mixture was then stirred at rt until the Mg had completely reacted (approximately 1 h). At this time THF (200 mL) and CuI (369 mg, 1.938 mmol) were quickly added, and the black reaction mixture was cooled to −78 °C with stirring under N_2. A solution of enone **1**[9] (2.529 g, 0.00930 mol), *N,N′*-dimethyl-*N,N′*-propyleneurea[22] (DMPU; 2.5 mL, 2.65 g, 0.0207 mol), and trimethylsilyl chloride (7.08 mL, 6.06 g, 0.0558 mol) in THF (10 mL) was then slowly added. The mixture was stirred at −78 °C under N_2 for 4.5 h, at which time NaOAc solution (10 mL) was added. The flask was removed from the cooling bath, allowed to warm to rt with stirring, and the brown supernatant was decanted. The precipitate was rinsed with ether, combined with the original supernatant, diluted with 1 L of ether, washed with water (6 × 100 mL) and $NaHCO_3$ solution (100 mL), and dried. Removal of solvent in vacuo left the crude product which was purified by flash chromatography[21] (silica gel, 3:1 petroleum ether/ether) to provide the adduct (1.831 g, 63%) as a pale yellow liquid, which was isolated as a 2.9:1 mixture of α:β isomers. Physical constants for the β isomer (**2b**) are reported separately above, while those for the α isomer (**3b**) are as follows: IR ($CHCl_3$) 3070 (w), 1730 (s), 1650 (w), 1460 (m), 1302 (m), 1192 (m), 1125 (s), 836 (s), 777 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08, 0.09 (both s, 3 H each, $SiMe_2$), 0.92 (s, 9 H, *t*-Bu), 1.76 (dd, 3 H, $J_{Me,vinyl\ H}$ = 1.4 Hz, $J_{Me,vinyl\ H}$ = 0.9 Hz, Me of isopropenyl), 2.52 (dd, 1 H, J_{gem} = 13.5 Hz, $J_{1,2\beta}$ = 2.2 Hz, H-2β), 2.53 (dd, 1 H, $J_{1,2\alpha}$ = 11.9 Hz, $J_{2\alpha,4}$ = 1.1 Hz, H-2α), 3.47 (ddd, 1 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 1.6 Hz, H-5), 3.52 (s, 3 H, OMe), 3.88 (dd, 1 H, J_{gem} = 11.4 Hz, H-6a), 3.91 (dd, 1 H, H-6b), 3.96 (d, 1 H, H-4), 4.01 (dddd, 1 H, $J_{1,vinyl\ H}$ = 0.9 Hz, $J_{1,vinyl\ H}$ = 0.4 Hz, H-1), 4.88 (ddq, 1 H, J_{gem} = 1.4 Hz, one vinyl H), 5.01 (ddq, one vinyl H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.2 and −5.4 ($Si(Me)_2$), 18.1 (vinyl Me), 18.3 (quaternary C of *t*-Bu), 25.8 (3 Me of *t*-Bu), 46.7 (CH_2 of ring), 59.7 (OMe), 62.4 (C-6), 80.4 (C-5), 81.4 (C-4), 81.5 (C-1), 112.0 (vinyl CH_2), 143.3 (quaternary vinyl C), 206.8 (C=O); MS *m/e* (no molecular ion) 257, 225, 197, 161 (base), 117, 95, 89; exact mass for $C_{12}H_{21}O_4Si$ (M^+ − *t*-Bu) calcd 257.1209, found 257.1202.

Acknowledgment. Financial support of this work by RUI Research Grant CHE-8700399 from the National Science Foundation is gratefully acknowledged. The work of K.S. was partially supported by a Council on Undergraduate Research Academic–Industrial Undergraduate Research Partnership (CUR-AIURP) award from the SmithKline Beecham Company. We are grateful to Professor Kosta Steliou (University of Montreal) for providing a copy of MODEL, and to him and Professor Dennis Liotta (Emory University) for advice in its use. The advice and assistance of Messrs. J. Blackburn, B. Brighton, and D. Gilliam of Hendrix College Computer Services is appreciated. Nomenclature advice was provided through the courtesy of Drs. Pat Giles and K. L. Loening of Chemical Abstracts Service. The mass spectral data were provided by the Midwest Center for Mass Spectrometry, at the University of Nebraska—Lincoln, a National Science Foundation-supported Regional Instrumentation Facility.

Registry No. 1, 84010-45-7; **2a**, 84010-40-2; **2b**, 139015-69-3; **3a**, 139015-68-2; **3b**, 139015-70-6; **13**, 139015-71-7; **14**, 139163-30-7; 2-bromopropene, 557-93-7.

(22) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

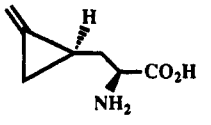
Synthesis of Enantiomerically Pure [(Methylenecyclopropyl)acetyl]-CoA: The Causative Agent of Jamaican Vomiting Sickness

Ming-tain Lai, Eugene Oh, Younan Shih, and Hung-wen Liu*

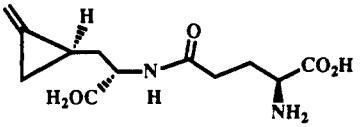
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received September 20, 1991

Hypoglycin A (**1**), together with its γ-glutamyl conjugate (hypoglycin B, **2**), was first isolated by Hassal and Reyle from the arillus and seeds of unripe ackee (*Blighia sapida*) in 1955.[1] It is an L-amino acid consisting of only seven carbons, albeit with an unusual methylenecyclopropyl moiety. While ripe ackee fruit serves as a dietary staple in Jamaica, ingestion of hypoglycin from unripe fruit is responsible for the Jamaican vomiting sickness.[2] The



HYPOGLYCIN A (*1*)



HYPOGLYCIN B (*2*)

actual causative agent has been identified as (1*R*)-[(methylenecyclopropyl)acetyl]-CoA (MCPA-CoA, **3**) which is derived in vivo from hypoglycin in three enzymatic steps.[3]

(1) (a) Hassal, C. H.; Reyle, K. *Biochem. J.* **1955**, *60*, 334. (b) Fowden, L.; Pratt, H. M. *Phytochemistry* **1973**, *12*, 1677.

(2) (a) Tanaka, K. In *Handbook of Clinical Neurology*; Vinken, P. J., Bruyn, G. W., Eds.; Elsevier-North Holland: Amsterdam, 1979; Vol. 37, Chapter 17, p 511. (b) Stuart, K. L. In *Hypoglycin*; Kean, E. A., Ed.; Academic: New York, 1975; p 39. (c) Osmundsen, H. *Trends Pharm. Sci.* **1986**, *7*, 186. (d) Tanaka, K.; Ikeda, Y. In *Fatty Acid Oxidation; Clinical, Biochemical, and Molecular Aspects*; Tanaka, K., Coates, P. M., Eds.; Alan R. Liss, Inc.: New York, 1990; p 167.

0022-3263/92/1957-2471$03.00/0