so long as decomplexation is not an important side reaction, the iron carbonyl moiety and the remaining bridgehead hydrogen will always bear a cis relationship to one another, and this relationship is carried through to products. In the penultimate step, a hydride is returned from the $-HFe(CO)_3$ moiety to the bridgehead to secure the cis fusion of the bicyclic hydrocarbon, as in **19.**

A similar argument can be applied to the trans isomer **15**; in all complex intermediates, the remaining bridgehead hydrogen bears a trans relationship to the attached iron species, and trans-fused products result. It is also possible to account for the temperature effect regarding **15** in terms of this mechanistic picture. At lower temperatures, complexes such as **20** possess sufficient stability to survive decomplexation; hence the hydrocarbon **9** is not produced. The limits of this stability are presumably exceeded at refluxing hexane temperature, and **9** is observed among rearrangement products. It is puzzling, in terms of such an argument, why **8** shows no such temperature effect. The complex **18** would be expected to be more stable than **20** because of steric effects; hence it should have more readily survived in the low-temperature case. Yet the hydrocarbon **9** was observed regardless of reaction temperature.

An intriguing alternative explanation for these results involves intermediate complexes which leave bridgehead hydrogen atoms intact. While such intermediates would be sterically difficult to attain from the cis complex **16,** similar problems are not present in **21**; hence a species such as **22** might be achievable. Nonallylic intermediates have been considered in iron carbonyl induced rearrangements of vinyl cyclopropanes.[11] We are actively pursuing labeling studies to distinguish between these alternative possibilities.

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(6) Prepared by the sequence *cis*-cyclooctene + ethyl diazoacetate → 9-carbethoxybicyclo[6.1.0]nonane → 9-hydroxymethylbicyclo[6.1.0]nonane → bicyclo[6.1.0]nonane-9-carboxaldehyde → tosylhydrazone → **8.** NMR and IR spectral data were consistent with structure **8,** and the chemistry of **8** agreed with that described by van Tamelen and co-workers.[7]
(7) Radlick, P.; Klem, R.; Spurlock, S.; Sims, J. J.; van Tamelen, E. E.; Whitesides, T. *Tetrahedron Lett.* **1968,** 5117–5121.
(8) The mixture of hydrocarbons was separated into its components most conveniently by column chromatography using $AgNO_3$–silica gel, monitored by GC. Compound **9** was identified from its ^1H NMR spectrum and thermal isomerization to 1-vinylcyclooct-1-ene, and **10** from its ^1H and ^{13}C NMR spectra. Compounds **11** and **12** could not be separated under any circumstances. A combination of ^1H and ^{13}C NMR spectra and catalytic hydrogenation to a single hydrocarbon, **13,** limited the possibilities to **11, 12,** bicyclo[6.2.0]dec-4-ene, and bicyclo[6.2.0]dec-1(8)-ene; the last two possibilities were eliminated by independent synthesis in the former case, and ^1H NMR spectra in the latter.
(9) Synthesized in low yield by the sequence *trans*-cyclooctene + dichloroketene → *trans*-10,10-dichlorobicyclo[6.2.0]decan-9-one → *trans*-bicyclo[6.2.0]decan-9-one → tosylhydrazone → **15** + **8** + **9,** followed by separation on $AgNO_3$–silica gel. Spectral data of **15** agree with those reported previously.[7]
(10) Manuel, T. A. *J. Org. Chem.* **1962** *27,* 3941–3945. Arnet, J. E.; Pettit, R. *J. Am. Chem. Soc.* **1961,** *83,* 2954–2955. Emerson, G. F.; Pettit R. *Ibid.* **1962,** *84,* 4591–4592.
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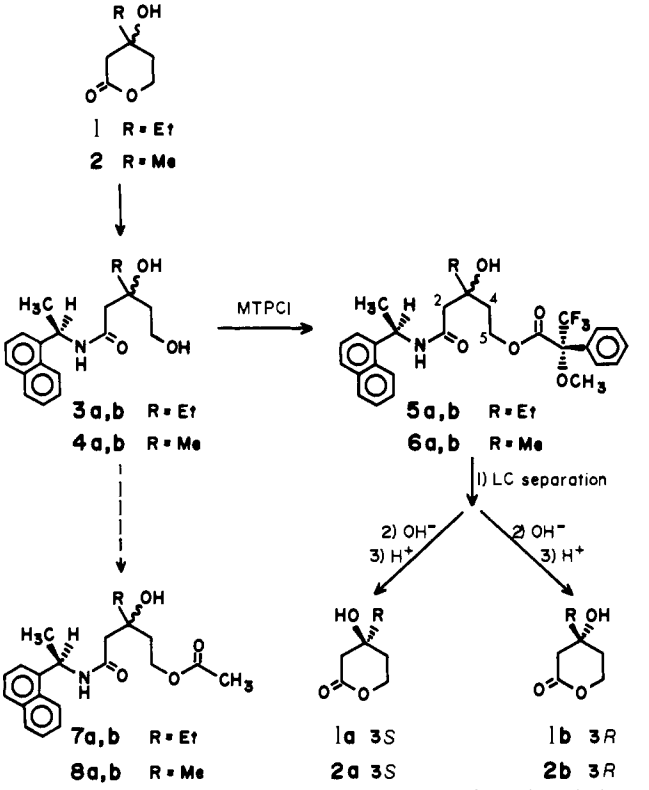
Absolute Configuration of Homomevalonate and 3-Hydroxy-3-ethylglutaryl and 3-Hydroxy-3-methylglutaryl Coenzyme A, Produced by Cell-Free Extracts of Insect Corpora Allata. A Cautionary Note on Prediction of Absolute Stereochemistry Based on Liquid Chromatographic Elution Order of Diastereomeric Derivatives

Sir:

Homomevalonate (HMev)[1] and 3-hydroxy-3-ethylglutarate (HEG)[2] have been implicated as probable intermediates in insect juvenile hormone (JH) biosynthesis. While the congeneric intermediate, mevalonate (Mev), has been shown to have the 3*R* configuration common to other organisms,[1b] no direct evidence has yet been presented for the absolute configuration of HMev or HEG (as its coenzyme A (CoA) ester). We report herein our findings with respect to the latter two compounds. We also confirm the 3*S* absolute stereochemistry of the Mev precursor 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), whose prior assignment rested solely on enzymological conversions.[3]

Racemic homomevalonolactone[1a] (HMev>, **1**) was converted via Scheme I in 30–40% overall yield into the 1-amido-5 esters **5a,b** by (1) heating with neat 1-(+)-α-(1′-naphthyl)ethylamine, and (2) treatment with a pyridine solution of the acyl chloride of (+)-α-methoxy-α-trifluoromethylphenylacetic acid. These diastereomers were then separated by micropreparative liquid chromatography (LC) into stereoisomerically pure components.[4,5] Each diastereomer (4–6 mg) was then analyzed by 90-MHz ^1H NMR and spectra were compared with those obtained from the similarly prepared derivatives **6a,b** of (3*R*)- and (3*S*)-mevalonolactone (Mev>, **2**).[4-6] Strong correlations were observed between chemical shift of diagnostic NMR resonances (Table I) for each pair of HMev vs. Mev derivatives according to their elution order on LC. Each of these four derivatives was then converted into the parent lactone of high enantiomeric purity via base hydrolysis

Scheme I[a]



[a] For diastereomeric derivatives, **a** = fast eluting and **b** = slow-eluting on LC.

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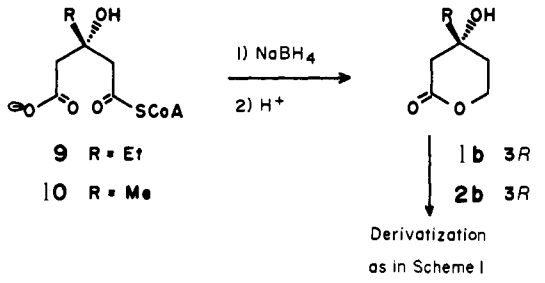
Table I. Chemical Shifts, δ (J in Hertz), of Diagnostic NMR Resonances for Diastereomers **5a,b** and **6a,b** (Scheme I) in $CDCl_3$ Solution

positional assignment of proton	fast eluting (**6a**, 3*S*)	slow eluting (**6b**, 3*R*)	fast eluting (**5a**)	slow eluting (**5b**)
C-4	1.87 (t, 2, J = 6)	1.84 (t, 2, J = 7)	1.87 (t, 2, J = 7)	1.83 (t, 2, J = 7)
C-2	2.21, 2.14 (2s, 2)	2.03, 1.95 (2s, 2)	2.19, 2.18 (2s, 2)	1.97, 1.94 (2s, 2)
$-OCH_3$	3.48 (d, 3, J = 1)	3.42 (d, 3, J = 2)	3.48 (d, 3, J = 1)	3.39 (d, 3, J = 1)
C-5	4.47, 4.46 (2t, 2, J = 6)	4.44, 4.40 (2t, 2, J = 7)	4.43 (t, 2, J = 8)	4.43, 4.36 (2t, 2, J = 7)

Scheme II



and acid workup. After chromatographic purification, the lactones were analyzed by induced circular dichroism spectroscopy in a CCl_4 solution of 10^{-4} M Cu(hexafluoroacetylacetonate)$_2$ as described by Dillon and Nakanishi.[7] HMev **1b** and (3*R*)-Mev **2b** each gave a positive Cotton effect;[8] conversely, negative Cotton effects[8] were seen for HMev **1a** and Mev **2a.** Thus, both NMR and CD data[9] indicate complete congruence of elution order with absolute configuration at C-3 between the homologous pairs of diastereomeric derivatives **5a,b** and **6a,b.**

LC analysis of derivatized [^{14}C]HMev (Scheme I), obtained from cell-free extracts of *Manduca sexta* corpora cardiaca–corpora allata (cc–ca) incubated with radiolabeled propionyl CoA (Pr-CoA) and acetyl CoA (Ac-CoA) plus appropriate cofactors, shows the label to coincide with the *slower* eluting diastereomer **5b,** proving that the parent lactone has in fact the 3*R* configuration, identical with that reported for Mev.[1,6]

Following the elucidation of the stereochemistry of HMev, we applied similar methodology to determine the absolute configuration of HEG-CoA and HMG-CoA, the expected metabolic precursors of HMev and Mev, respectively. Earlier we identified the achiral metabolites, 3-hydroxy-3-methyl- and 3-hydroxy-3-ethylglutaric acids, obtained on base hydrolysis of cc–ca enzymatic products of Ac-CoA and Pr-CoA.[2] More recently, we developed a new method for separation of acyl CoA thioesters by reversed-phase ion-pair chromatography.[10] Using this technique, we have separated products formed by incubation of cc–ca enzymes with [1-^{14}C]Ac-CoA and Pr-CoA, and find that two of several radiolabeled components in fact coelute with synthetic (3*R,S*)-HMG-CoA and (3*R,S*)-HEG-CoA standards (detectable by UV monitoring at 254 nm). The biosynthetic, labeled zones corresponding to HMG- and HEG-CoA were isolated and subjected to microchemical transformations (Scheme II). Reductive cleavage of the thioester moiety with $NaBH_4$ according to the method of Barron and Mooney[11] proved to be regiospecific,[12] affording only one antipode of mevalonate using stereochemically pure [^{3}H]HMG-CoA as a model substrate. Analysis by LC of the derivatives of [^{14}C]HMev and [^{14}C]Mev formed via Schemes II and I from the biosynthesized HEG- and HMG-CoA showed the radiolabel to reside exclusively (>99%) in the *slower* eluting 3*R* diastereomer in each case, establishing the 3*S* configuration for both HEG-CoA and HMG-CoA.[13] These data provide chemical confirmation of the prior assignment[3] for (3*S*)-HMG-CoA based on enzymological conversion into (3*R*)-Mev. Further, the absolute configuration of the homologous intermediates (3*S*)-HEG-CoA and (3*R*)-HMev are in accord with the conventional stereochemistry of mammalian and plant isoprenoid precursors.

In light of recent reports in the literature[14] regarding correlations between absolute configuration and chromatographic elution order of model diastereomers, our previous data[1b] suggested the possibility of the stereochemistry of HMev to be the *opposite* of that above demonstrated. However, on rigorous reexamination of derivatized biosynthetic [^{14}C]HMev and [^{14}C]Mev, we have found a surprising reversal of elution order on LC analysis. Namely, the HMev amido acetates **7a,b** show an inverse elution order (3*R* before 3*S*) compared with the corresponding Mev amido acetates **8a,b.** No such inversion was observed for the HMev amido MTP esters **5a,b** vs. the analogous Mev derivatives **6a,b;** for each pair the 3*S* diastereomer elutes before 3*R*.

These data vividly illustrate the difficulties inherent in assigning absolute configurations of even very closely related structures (substitution of ethyl for methyl) based *solely* upon chromatographic elution order,[14] a point that we have raised elsewhere, citing a less dramatic example.[15]

Acknowledgments. We thank M. S. Hall for providing corpora cardiaca–corpora allata gland complexes from *Manduca sexta,* R. Records (Stanford University) for determining CD spectra, Dr. M. Maddox (Syntex) for measuring NMR spectra, Professor C. J. Sih for samples of authentic (*R*)- and (*S*)-mevalonolactone, and the National Science Foundation for partial financial support (PCM 76-15686).

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(4) Diastereomeric purity of HMev derivatives **5**: peak **a** (faster eluting), 99.4%; peak **b** (slower eluting), 98.6%. Diastereomeric purity of Mev derivatives **6**: peak **a** (faster eluting), ≥99.8%; peak **b** (slower eluting), ≥99.5%.
(5) LC analysis conditions: Zorbax-SIL column, 22 × 0.79 cm eluted with 20% ethyl acetate in pentane, 75% water saturated, at 5 mL/min.
(6) The assignment of absolute configuration of Mev derivative **6a** as 3*S* and **6b** as 3*R* was accomplished by derivatization of samples of authentic (3*S*)- and (3*R*)-mevalonolactone kindly supplied by Professor C. J. Sih: F.-C. Huang, L. F. Hsu Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, *J. Am. Chem. Soc.*, **97,** 4144–4145 (1975).
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(8) CD (CCl_4), λ (θ): **1b,** 0.87 mg/mL, 334 (+0.35), 325 (+0.27); **2b,** 0.37 mg/mL, 333 (+0.75), 321 (+0.51); **1a,** 1.08 mg/mL, 333 (−0.30), 321 (−0.25), 308 (−0.26); **2a,** 1.05 mg/mL, 334 (−0.28), 320 (−0.24), 305 (−0.29).
(9) Examination of space-filling models of the lactones show that bulk relationships appear to be consistent with predicted[7] sign of Cotton effect in all cases. However, these tertiary alcohols have relatively slight differences in steric bulk of their three substituent groups. The model predictions would not have been compelling in the absence of data correlating our sample to mevalonolactones of known configuration.[6]
(10) F. C. Baker and D. A. Schooley, *Anal. Biochem.*, **94,** 417–424 (1979).
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(12) Stereochemically pure [^{3}H]HMG-CoA was generated[3b] by prolonged action of insect HMG-CoA reductase enzyme on (3*R,S*)-[^{3}H]HMG-CoA. The unused substrate (presumably (3*R*)-[^{3}H]HMG-CoA) was reduced with $NaBH_4$, acidified, and worked up and the chiral mevalonolactone analyzed as in Scheme I. Only (3*S*)-[^{3}H]Mev was observed, proving that (a) all of the natural antipode of HMG-CoA had been enzymatically consumed and (b) no racemization occurred in the analytical scheme. Earlier, we attempted aminolysis of chiral [^{3}H]HMG-CoA or its monomethyl ester (diazomethane) with 1-(+)-α-(1′-naphthyl)ethylamine. LC separation of the monomethyl esters of the HMG mononaphthylethylamide revealed varying degrees of racemization to occur during aminolysis.

(13) The sequence rule mandates the somewhat confusing difference in stereochemical nomenclature in this substrate-product relationship.
(14) (a) G. Helmchen, H. Völter, and W. Schühle, *Tetrahedron Lett.*, 1417–1420 (1977); (b) G. Helmchen, G. Nill, D. Flockerzi, W. Schühle, and M. S. K. Youssef, *Angew. Chem., Int. Ed. Engl.*, **18**, 62–63 (1979); (c) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 1839–1844 (1977); (d) W. H. Pirkle and D. L. Sikkenga, *J. Chromatogr.*, **123**, 400–404 (1976). These reports are concerned with model amides[14a,b] or carbamates[14c,d] in which a single polar functional group is present, and the chiral center is always α to the polar group. In our diastereomeric derivatives, three polar functional groups capable of interacting with the adsorbent are present, and the chiral center is β to the amide functionality. Thus, the conformation of diastereomers **5–8a,b**, in solution or adsorbed, is less susceptible to definition than the simpler literature models.
(15) B. J. Bergot, R. J. Anderson, D. A. Schooley, and C. A. Henrick, *J. Chromatogr.*, **155**, 97–105 (1978).

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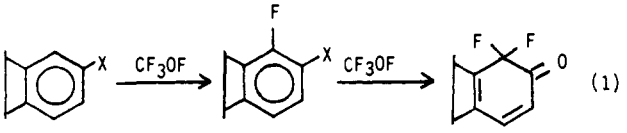
Addition–Elimination Reactions of CF_3OF with Activated Aromatics

Sir:

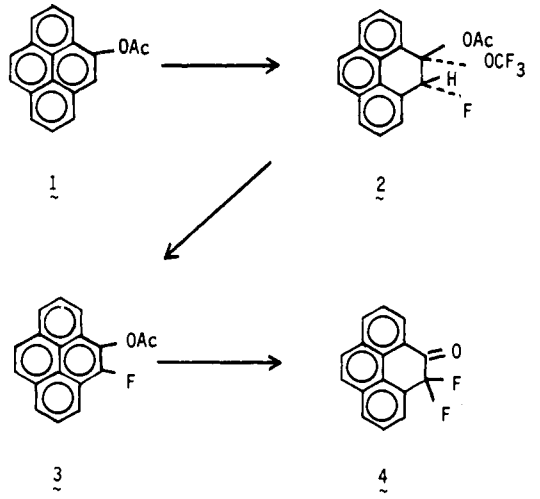
The literature contains a number of examples of fluorination of aromatic compounds with fluoroxytrifluoromethane (CF_3OF). The CF_3OF fluorination of activated aromatic systems can be controlled to produce either monofluoro or *gem*-difluoro products, depending on the amount of CF_3OF used (eq 1).[1-8]



(1)

While the path for difluorination is known to involve electrophilic addition of CF_3OF to the monofluoro intermediate,[4] the route for monofluorination is still uncertain. Monofluorination could occur by (a) electrophilic substitution, (b) free-radical substitution, or (c) addition–elimination.[1,3]

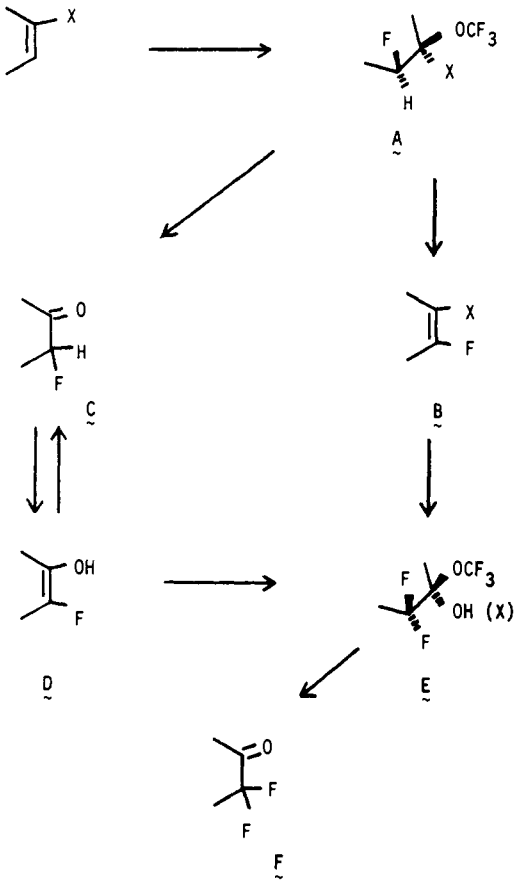
In our studies of the reaction of activated aromatics with CF_3OF,[7,8] we have employed 4-acetoxypyrene (**1**) as a



mechanistic probe. 4-Acetoxypyrene is especially suitable since it can give stable products from (a) electrophilic substitution[9,10] at the 1 or 5 positions, (b) free-radical dimerization,[11] and (c) molecular addition to the 4,5 position.[9]

Reaction of 4-acetoxypyrene[10] with slightly less than 1 equiv of CF_3OF[12] at −78 °C in methylene chloride furnished a green oil from which were isolated 67% unreacted 4-acetoxypyrene and 27% (82% yield) adduct **2** as a semisolid:[13,14] ^1H NMR

Scheme I



($CDCl_3$) δ 7.70–8.60 (m, arom), 6.62 (d, 1 H, CHF, J = 96 Hz), 2.75 (s, 3 H, CH_3); ^{19}F NMR ($CDCl_3$) ϕ* 57.4 (s, 3 F, CF_3O), 57.6 (d, 1 F, CHF, J = 96 Hz); ^{13}C NMR ($CDCl_3$) δ 209.5 (s, C=O), 200.5 (q, CF_3, J = 199.6 Hz), 125.8 (d, CF, J = 188.5 Hz), 125–130.3 (m, arom), 17.5 (s, CH_3); IR (neat) 1760 cm^{-1} (C=O), 1100–1300 (CF_3O); MS (80 eV) *m/e* 364 amu (calcd mol wt 364). On standing at room temperature for several days, adduct **2** slowly converted into 5-fluoro-4-acetoxypyrene (**3**):[14] ^1H NMR ($CDCl_3$) δ 7.5–8.5 (m, arom), 2.7 (s, CH_3); ^{19}F NMR ($CDCl_3$) ϕ* 57.2 (s); MS *m/e* 262 amu (calcd mol wt 262); mp 76–79 °C. Extended reaction of **1** or **3** with CF_3OF at −78 °C in CH_2Cl_2 furnished a mixture from which 5,5-difluoro-4-(5*H*)-pyrenone (**4**)[14] was obtained in 20% yield: ^1H NMR ($CDCl_3$) δ 6.3–7.95 (m, arom); IR (KBr) 1690 cm^{-1} (C=O); ^{19}F NMR ($CDCl_3$) ϕ* 101.0 (s); MS *m/e* 256 amu (calcd mol wt 256); mp 117–120 °C. In a control experiment, 2-acetylaminopyrene,[15] which has an extremely activated 1 position toward electrophilic substitution, failed to give any isolable fluorinated products on reaction with CF_3OF.

Compound **2** represents the first report of a 1:1 adduct between CF_3OF and an activated aromatic system. The isolation of **2** and its conversion to **3** conclusively show that monofluorination occurs by addition of CF_3OF to the aromatic system prior to elimination. Further fluorination of the monofluoroaromatic with CF_3OF produces difluoro products. The pathway illustrated in Scheme I accounts well for all of he experimental data reported.[1-8]

In this scheme, CF_3OF adds to the activated bond to give A which can either eliminate CF_3OH to give B or undergo oxidation–hydrolysis to give C ⇌ D. Previous work has shown that sterically hindered systems, e.g., benzo[*c*]phenanthrene and 7,12-dimethylbenz[*a*]anthracene, prefer existence as the keto tautomer (C).[8] The difluoro ketone F is obtained through further addition of CF_3OF to B or D to produce E which in turn is oxidized or hydrolyzed to F.[4,7]

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