sealed tube at 85 °C. The reaction mixture was evaporated and analyzed by ^{1}H NMR (400 MHz). On a preparative run **20C** (100 mg) was treated as above at 100 °C for 20 days. Preparative TLC (10% MeOH/$CHCl_3$) gave a pure mixture of **21** and **22** (100 mg, 72%) as a colorless oil.

21: ^{1}H NMR 7.8–7.2 (m, 14 H), 4.22 (dd, J = 2.9, 10.5 Hz, 1 H), 3.69 (d, J = 13.1 Hz, 1 H), 3.59 (d, J = 13.1 Hz, 1 H), 3.06 (dd, J = 10.5, 13.5 Hz, 1 H), 2.91 (dd, J = 2.9, 13.1 Hz, 1 H), 2.39 (s, 3 H); ^{13}C NMR (in part) 65.15, 57.05, 51.31, 21.27; MS 350 ((M + H)$^+$, 25%), 210 (50%), 91 (100%); HRMS calcd for $C_{22}H_{24}NOS$ 350.1579, found 350.1646.

22: ^{1}H NMR (in part) 3.83 (d, J = 13.1 Hz, 1 H), 3.79 (d, J = 13.1 Hz, 1 H), 3.18 (m, 1 H), 2.91 (dd, J = 4.6, 13.3 Hz, 1 H), 2.86 (dd, J = 7.9, 13.3 Hz, 1 H); ^{13}C NMR (in part) 65.54, 58.81, 51.16, 21.27.

Conversion of 21 to (+)-(*R*)-*N*-Benzyl-(1-phenylethyl)-amine. A mixture of **21** and **22** (5:1, 363 mg) in ethanol (5 mL) was treated with Raney nickel as described above. Purification by acid extraction and then column chromatography (silica gel, EtOAc/hex 1:1) gave pure (+)-(*R*)-*N*-benzyl-*N*-(1-phenylethyl)-amine as a colorless oil (68 mg): $[\alpha]^{25}_D$ +23.7 (*c* 1.35, EtOH), lit.[27] +56.2 (*c* 1.07, EtOH); ^{1}H NMR (in part) 3.8 (q, J = 6.6 Hz, 1 H), 3.65 (d, J = 13.1 Hz, 1 H), 3.58 (d, J = 13.1 Hz, 1 H), 1.36 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (in part) 57.4, 51.6, 24.4; MS 212 ((M + H)$^+$, 45%), 154 (100%).

Diethyl (*IS*,*SR*)-[1′Phenyl-2′-(*p*-tolylsulfinyl)ethyl]-malonate (23) and (*IR*,*SR*)-24. To a solution of diethyl malonate (190 mg, 1.2 mmol) in THF (0.5 mL) at −78 °C under nitrogen was added nBuLi (0.49 mL, 0.78 mmol, 1.6 M in hexane). The mixture was warmed to room temperature, and **20C** (100 mg, 0.4 mmol) in THF (0.5 mL) was added. The solution was refluxed for 6.5 days and then cooled to room temperature. CH_2Cl_2 (50 mL) was then added, and the solution was washed with saturated NH_4Cl solution (2 × 25 mL), dried, and evaporated. The ratio of **23** and **24** was determined by ^{1}H NMR (400 MHz) on the crude reaction mixture. Column chromatography (EtOAc/hexane, 1:1) gave pure **23** (105 mg, 65%). The ^{1}H NMR spectral data for **23** and **24** were very similar to those reported by Tsuchihashi.[3c,d]

23: ^{1}H NMR 7.5–7.2 (m, 5 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.92 (dq, J = 2, 7.2 Hz, 2 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.56 (m, 1 H), 3.45 (dd, J = 8.7, 12.9 Hz, 1 H), 3.34 (dd, J = 5.5, 12.9 Hz, 1 H), 2.41 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 0.99 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 167.5, 167.3, 141.9, 138.9, 130.0, 128.6, 128.3, 127.8, 124.7, 61.7, 61.4, 57.3, 40.5, 21.4, 14.0, 13.7; MS 403 (20%, M + H$^+$).

24: ^{1}H NMR 7.5–7.2 (m, 9 H), 4.19 (m, 2 H), 4.07 (m, 1 H), 3.97 (q, J = 7.2 Hz, 2 H), 3.74 (d, J = 9.5 Hz, 1 H), 3.25 (dd, J = 3.8, 12.8 Hz, 1 H), 3.04 (dd, J = 11.6, 12.8 Hz, 1 H), 2.39 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.04 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 167.5, 167.0, 141.5, 138.4, 136.0, 129.9, 128.8, 128.6, 127.9, 124.0, 63.0, 61.7, 61.5, 57.6, 40.5, 21.3, 14.0, 13.8; MS 403 (30%, M + H$^+$).

Acknowledgment. Financial support by the Australian Research Grants Scheme is gratefully acknowledged. P.B. thanks the University of Wollongong for a B.Sc. (Hons) scholarship.

Registry No. 1, 109985-71-9; 1 (deformyl deriv), 110527-65-6; **2a**, 63268-43-9; **2b**, 123934-65-6; **2c**, 123934-66-7; **3**, 109985-72-0; **4**, 109985-73-1; **5**, 123934-62-3; **5** (R_1 = R_2 = R_3 = H), 2508-29-4; **6**, 123934-63-4; **7**, 123934-64-5; **8b**, 123934-67-8; **8c**, 123934-70-3; **9b**, 123934-68-9; **9c**, 123934-71-4; **10**, 109985-76-4; **11**, 109985-75-3; **12b**, 123934-72-5; **13b**, 123934-73-6; **13c**, 123934-69-0; **14**, 51745-28-9; **15a**, 124019-83-6; **15s**, 124019-84-7; **16a**, 124093-68-1; **16s**, 123934-74-7; **17a**, 124019-85-8; *syn*-**17** (isomer 1), 124019-86-9; *syn*-**17** (isomer 2), 124019-87-0; **18**, 67008-23-5; **19**, 497-88-1; **20I**, 41103-85-9; **20C**, 63268-44-0; **21**, 118653-58-0; **22**, 118620-49-8; **23**, 41103-88-2; **24**, 41379-03-7; $(MeO)_2P(O)CH_3$, 756-79-6; $PhCH_2NH_2$, 100-46-9; (*R*)-$PhCH(CH_3)NHCH_2Ph$, 38235-77-7; $CH_2(CO_2Et)_2$, 105-53-3; (−)-menthyl (*S*)-benzenesulfinate, 34513-32-1; (−)-menthyl (*S*)-2,4,6-triisopropylbenzenesulfinate, 124019-82-5.

Notes

Preparation of 3-Acetyl-2-hydroxyindoles via Rhodium Carbenoid Aromatic C–H Insertion[1]

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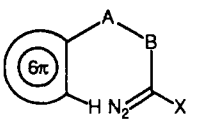
Received February 14, 1989

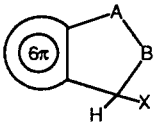
A number of recent reports have described the annulation of both five- and six-membered ring carbocycles[2] and five-membered ring heterocycles[3] into aromatic and heteroaromatic rings via rhodium carboxylate catalyzed decomposition of diazo compounds such as **1**.

We have described, in a 1987 communication, the preparation of 2-hydroxy-3-acetylfurans, example **d**



1

a: A = CH_2; B = C=O; X = H; 6π = phenyl
b: A = CH_2; B = CH_2C=O; X = H; 6π = phenyl
c: A = CH_2; B = SO_2; X = H, CO_2Et, $COCH_3$; 6π = phenyl, 2-thienyl
d: A = O; B = C=O; X = $COCH_3$; 6π = phenyl, naphthyl



2

above.[3b] These compounds exist in the furan form rather than as the tautomeric 3-acetylbenzofuran-2-ones. In this note, we report the extension of the insertion reaction to the preparation of 3-acetyl-2-hydroxyindoles **4** by reaction of the appropriate α-diazo anilides **3** with 5 mol % of Rh_2OAc_4 in refluxing benzene. The further extension of the cyclization reaction to the preparation of 2-hydroxyindoles bearing a CO_2Et group at C_3 of the indole or indoles bearing a strongly electron withdrawing group such as NO_2 was not successful. N-Unsubstituted indoles (R = H in

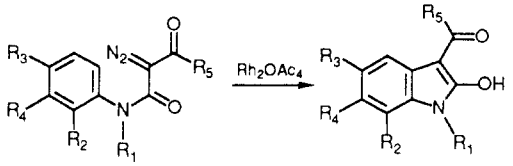
(1) Presented at the 8th Heterocyclic Chemistry Symposium, Heidelberg, Aug 1987.

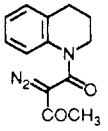
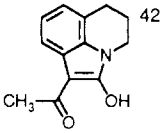
(2) (a) McKervey, M. A.; Russel, D. N.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 491. (b) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *Ibid.* **1984**, 129. (c) Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 165. (d) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479. (e) Taylor, E. C.; Davis, H. M. *Tetrahedron Lett.* **1983**, *24*, 5453.

(3) (a) Hrytsak, M.; Etkin, N.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679. (b) Hrytsak, M.; Durst, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1150. (c) Storflor, H.; Skramstad, J.; Nordenson, S. *Ibid.* **1984**, 208. (d) Jefford, C. W.; Zaslona, A. *Tetrahedron Lett.* **1985**, *26*, 6035.

0022-3263/90/1955-1093$02.50/0

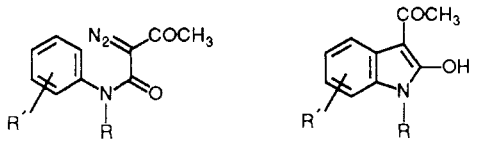
Table I. Rhodium Acetate Catalyzed Reactions of α-Diazo Anilides



	starting diazo compound					product indole, %
	R_1	R_2	R_3	R_4	R_5	
3a	CH_3	H	H	H	CH_3	77
3b	CH_3	CH_3	OCH_3	H	CH_3	77
3c	Ph	H	H	H	CH_3	87
3e	$PhCH_2$	H	H	Cl	CH_3	>95[a]
9	$PhCH_2$	H	H	NO_2	CH_3	(**10**) < 5
11	H	H	H	H	CH_3	(**12**) 7
14	CH_3	H	H	H	OEt	(**15**) 10
3d						42 

[a] Crude yield.

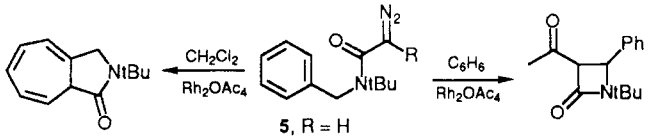
4) could not be prepared directly by this route; however, the *N*-benzyl-protected derivative (R = CH_2Ph, R′ = Cl in 4) was obtained.



3 **4**

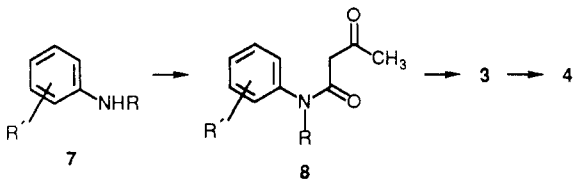
R = CH_3, Ph, CH_2Ph; R′ = H, CH_3, OCH_3, Cl

The formal aromatic C–H insertion process observed by us for the formation of **4** from **3** clearly differs from the ring expansion products[4] and the β-lactam formation[5] observed by Doyle and co-workers for the homologous α-diazo *N-tert*-butylbenzamides **5** and **6**, respectively. Isoquinolones (electrophilic aromatic substitution products) can be obtained from **5** by treatment with trifluoroacetic acid in methylene chloride at 25 °C.[6]



5, R = H
6, R = $COCH_3$

The diazo compounds required for this study were readily prepared by standard methodology. Thus, the aromatic amines **7** were treated with diketene to give the expected amides **8** which gave upon exposure to tosyl azide and triethylamine or NaH in THF[7] the desired α-diazo anilides **3**. These diazo compounds, when heated with 5 mol % of Rh_2OAc_4 in refluxing benzene for 1–5 h, produced the 3-acetylindoles **4a–e** in yields ranging from about 50 to 90%. (See Table I.)

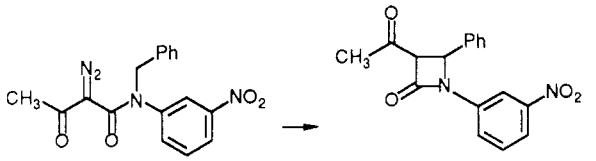


7 **8**

R = CH_3, Ph; R′ = H, CH_3, OCH_3

The hydroxyindole, rather than the 2-oxoindole structure, was readily apparent for the 3-acetyl derivatives. For example, the proton NMR spectra of the compounds **4a–d** each showed a low field signal at δ = 13.5–14 ppm due to the enolic hydrogen, while the infrared spectra displayed a strongly conjugated carbonyl frequency at 1650–1660 cm^{-1}. The carbon-13 spectra of these compounds included two peaks in the δ = 170–173 and 101–102 ranges, which were ascribed to carbons 2 and 3 of the indole ring, respectively.

Attempted cyclization of the *m*-nitro derivative **9** under the above reaction conditions with varying amounts of Rh_2OAc_4 caused disappearance of the starting material and formation of a large number of products. Thus far the only isolable product, obtained in <5% yield, has been tentatively identified as the β-lactam **10**. In view of the low reactivity of the nitro-substituted aromatic toward electrophilic substitution, the alternate modes of reaction of the rhodium carbenoid including insertion into the benzylic C–H bond occur.[5]



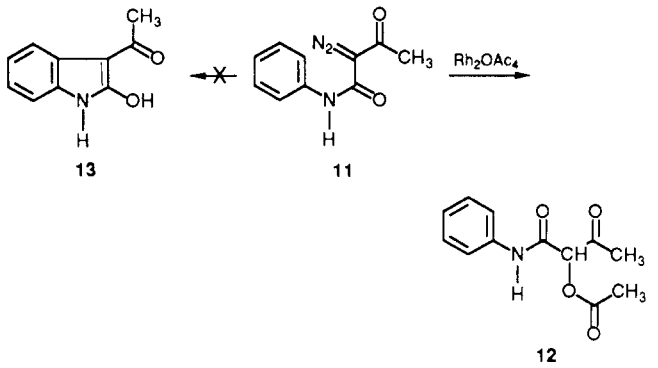
9 **10** (< 5%)

Disappointingly, the rather clean insertion reactions that lead to **4** when the nitrogen in the diazo compound **3** bore an alkyl or phenyl group could not be extended to compounds in which this substituent had been replaced by a hydrogen. Thus reaction of compound **11** prepared from aniline and diketene followed by diazo transfer, with Rh_2OAc_4 or $Rh_2(OCOCF_3)_4$ in CH_2Cl_2 at room temperature, proceeded quite slowly and afforded a myriad of products (TLC). In one experiment using 5–19 mol % of Rh_2OAc_4 as catalyst, a small amount (6%) of a compound identified as **12** (300-MHz NMR: δ 2.29 (s, 3 H), 2.45 (s, 3 H), 5.62 (s, 1 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.49 (d, *J* = 7.5 Hz, 2 H), and 7.98 (NH) ppm) was isolated. This compound may result from displacement of one of the acetate ligands in the catalyst by the amide function of **11**, followed by an intramolecular insertion of acetate into the Rh–carbenoid bond. Access to the desired parent indole **13** and analogues may be possible via hydrogenolysis of the N-benzylated derivatives such as **4e**.

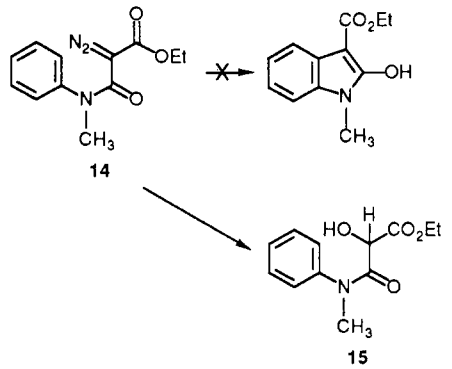
In the case of the diazo ester **14**, as with **9** and **11**, no aromatic CH insertion product analogous to **4** could be isolated from the many products formed. A small amount (12%) of product identified as the alcohol **15**, the result of trapping of the carbenoid by adventitious water present in the reaction mixture, was the only pure compound obtained.

Our results confirm that the course of the rhodium-catalyzed decomposition of α-diazo amides is highly dependent on the substituents surrounding the diazo function.[4-6] They suggest that the planning of a synthetic strategy using these compounds must be done with con-

(4) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639.
(5) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.
(6) Rhiston, G. M.; Schwartz, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643.
(7) Regitz, M.; Maas, G. *Aliphatic Diazo Compounds. Properties and Synthesis*; Academic Press: New York, 1987.



siderable caution, since the relatively small change from $COCH_3$ in the diazo compounds **3** to $CO_2CH_2CH_3$ in **14** completely destroys the annulation sequence.



Experimental Section

Preparation of β-Keto Amides 8. General Procedure. The anilines were mixed with 1.1 equiv of diketene and 10–20 mg of sodium acetate. The reaction mixture was then refluxed, either neat or as an acetone solution (1 mL/mequiv). These reactions can also be carried out in CH_2Cl_2 solution (1 mL/mequiv) at −20 °C, by using several drops of triethylamine as catalyst. The crude products obtained after removal of volatile materials on the rotary evaporator were purified by flash or preparative HPLC chromatography. The yields of purified product were generally above 95% except when aniline was used as the starting amine. The products were typically a mixture of ketone (δ for CH_3CO = 2.0) and enol (δ for $CH_3C(OH)$=C = 1.7) tautomers, with the former predominating by about a 3:1 ratio. These intermediates were not further characterized but converted into the corresponding diazo compounds **3**.

Diazo Transfer Reactions. To a solution of the keto anilides (2–7 mmol) and 2 equiv of triethylamine dissolved in 10 mL of acetonitrile was added 1.1 equiv of tosyl azide. The solution was stirred for 6–24 h. When the starting keto anilides had disappeared (TLC) the solvent was evaporated (bath temperature < 35 °C). The residue was dissolved in ether and washed successively with 10% NaOH solution and then H_2O. The crude α-diazo-β-keto anilides thus obtained were characterized by their rather simple proton NMR spectra, ms, and mp and then reacted directly with rhodium acetate.

Diazo compound 3a: 86%; oil; ^1H NMR δ 2.48 (s, 3 H), 3.33 (s, 3 H), 7.0–7.5 (m, 5 H); MS 217 (M^+, 2), 189 (M − 28, 100), 174 (66), 147 (M − 28 − 42, 93); IR 2180 (s), 1640 (vs) cm^{-1}.

Diazo compound 3b: 84%; mp 81–82 °C; ^1H NMR δ 2.20 (s, 3 H), 2.40 (s, 3 H), 3.17 (s, 3 H), 3.78 (s, 3 H), 6.5–7.2 (m, 3 H); MS 261 (M^+, 48), 233 (M − 28, 60), 218 (M − 28 − 15, 53), 191 (M − 28 − 42, 56), 43 (100); IR 2110 (s), 1635 (vs) cm^{-1}.

Diazo compound 3c: 52%; mp 94–95 °C; ^1H NMR δ 2.50 (s, 3 H), 7.0–7.5 (m, 10 H); MS 279 (M^+, 9), 251 (M − 28, 87), 236 (M − 28 − 15, 64), 209 (M − 28 − 42, 68), 180 (100); IR 2110 (s), 1655 (vs) cm^{-1}.

Diazo compound 3d: 85%; mp 60–61 °C; ^1H NMR δ 1.8–2.1 (m, 2 H), 2.39 (s, 3 H), 2.67 (t, J = 6 Hz, 2 H), 3.73 (t, J = 6.5 Hz, 2 H), 7.10 (s, 4 H); MS 243 (M^+, 11), 215 (M − N_2, 100), 200 (M − N_2 − CH_3, 62), 173 (M − N_2 − CH_2CO, 62); IR 2112 (s), 1650 (vs) cm^{-1}.

Diazo compound 3e: 95%; viscous oil; ^1H NMR δ 2.49 (s, 3 H), 4.93 (s, 2 H), 6.92 (m, 1 H), 7.08 (m, 1 H), 7.25 (m, 7 H); MS 301 (M + 2 − N_2, 25), 299 (M − 2, 71), 259, 257 (M − N_2 − CH_2CO, 19, 59); IR 2118 (s), 1650 (vs) cm^{-1}.

Diazo compound 9: 57% yellow oil; ^1H NMR δ 2.43 (s, 3 H), 5.01 (s, 2 H), 7.18–7.29 (m, 5 H), 7.37 (m, 1 H), 7.51 (t, J = 8.2 Hz, 1 H), 7.94 (t, J = 2.2 Hz, 1 H), 8.12 (m, 1 H); MS (CI/ether) 339 (M + 1, 81), 311 (M + 1 − N_2, 98), 281 (M + 1 − N_2 − NO, 61), 269 (M + 1 − N_2CH_2CO, 42); IR 2121 (s), 1665 (vs) cm^{-1}.

Diazo compound 11 was prepared in 76% yield, using 2.6 equiv of NaH and 1 equiv of tosyl azide in THF for 1 h. ^1H NMR: δ = 2.36 (s, 3 H), 7.3 (m, 5 H), 10.13 (br NH). IR: 3250 (br), 2127, 1666 cm^{-1}.

Diazo compound 14: 60%; oil; ^1H NMR δ 1.13 (t, J = 7 Hz, 3 H), 3.40 (s, 3 H), 4.03 (q, J = 7 Hz, 2 H), 7.0–7.5 (m, 511); MS 247 (M^+, 1), 219 (M − 28, 5), 77 (100); IR 2127 (s), 1724 (vs) cm^{-1}.

Rhodium Acetate Catalyzed Insertion Reactions of the Diazo Compounds 4. General Procedure. The α-diazo-β-keto amides (200 mg) were dissolved in 10–20 mL of benzene. The solution was boiled until approximately half the solvent had evaporated, in order to azeotrope off any water. Rhodium acetate (5 mol %) was then added and the solution was refluxed under N_2 for 1–5 h. The crude 3-acetyl-2-hydroxyindoles were purified by flash chromatography.

4a: 77%; mp 107–108 °C; ^1H NMR δ 2.44 (s, 3 H), 3.33 (s, 3 H), 6.94 (d, 1 H), 7.09 (t, 1 H), 7.21 (t, 1 H), 7.36 (d, 1 H); ^{13}C NMR δ 20.3, 25.6, 101.8, 108.3, 119.6, 122.1, 122.2, 125.2, 138.8, 171.0, 172.8; HR-MS M^+ calcd 189.0788, found 189.0785. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.39; N, 6.13.

4b: 77%; mp 140–141 °C; ^1H NMR δ 2.41 (s, 3 H), 2.57 (s, 3 H), 3.57 (s, 3 H), 3.79 (s, 3 H), 6.49 (d, J = 2.5 Hz, 1 H), 6.78 (d, J = 2.5 Hz, 1 H); ^{13}C NMR δ 19.3, 20.4, 28.9, 55.7, 101.7, 104.4, 113.6, 120.7, 123.8, 130.8, 154.9, 171.1, 173.0; HR-MS M^+ calcd 233.1050, found 233.1031.

4c: 87%; mp 106–107 °C; ^1H NMR δ 2.51 (s, 3 H), 6.9–7.5 (m, 9 H); ^{13}C NMR 20.7, 101.6, 109.7, 119.8, 122.2, 122.5, 125.1, 126.6, 128.0, 129.5, 133.9, 138.6, 170.5, 173.9; HRMS M^+ calcd 251.0945, found 251.0957.

4d: 42%; mp 158–155 °C; ^1H NMR δ 2.05 (quint, J = 6 Hz, 2 H), 2.42 (s, 3 H), 2.82 (t, J = 6 Hz, 2 H), 3.82 (t, J = 6 Hz, 2 H), 6.9–7.2 (m, 3 H); ^{13}C NMR δ 20.2, 21.4, 24.7, 38.5, 102.5, 117.4, 120.3, 120.6, 121.5, 123.7, 134.8, 169.7, 172.6; HRMS M^+ calcd 215.0945, found 215.0932.

4e: >95% crude; 136.5–137 °C, from CH_2Cl_2–hexane; ^1H NMR δ 2.05 (s, 3 H), 4.58 (s, 2 H), 6.34 (s, 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 6.8–6.9 (m, 6 H); ^{13}C NMR δ 21.2, 43.1, 100.7, 109.6, 120.2, 121.4, 121.9, 127.1, 127.7, 128.9, 130.2, 135.7, 138.5, 170.8, 175.3; HR-MS M^+ calcd 299.0713, found 299.0697.

Reaction of 9 with Rh_2OAc_4. Diazo compound **9** (210 mg) was dissolved in 10 mL of freshly distilled benzene. The solution was brought to reflux and Rh_2OAc_4 (12 mg) was added. The solution was refluxed until the TLC showed no remaining starting material (1 h). The reaction mixture was filtered, evaporated, and chromatographed on silica gel. Elution with 3.5:1 hexane–ethyl acetate afforded 4.5 mg of a fraction tentatively identified as **10**. ^1H NMR peaks at δ 2.39 (s, 3 H), 4.22 (d, J = 2.7 Hz, 1 H), 5.52 (d, J = 2.7 Hz, 1 H), 7.35–7.4 (m, 6 H), 7.55 (d of m, J = 8.2 Hz, 1 H), 7.90 (d of m, J = 8.2 Hz, 1 H), 8.06 (t, J = 2.2 Hz, 1 H). No other pure products were obtained.

Reaction of 11 with Rh_2OAc_4. Compound **11** (0.15 g) was dissolved in 20 mL of benzene. Approximately 7 mL was removed via distillation and then 30 mg of Rh_2OAc_4 (~10 mol %) was added and the reaction mixture was refluxed for 2 h. The crude product was separated on a Chromatatron, using 4:1 hexane/ethyl acetate. The yield of compound **12** was 12 mg (7%): ^1H NMR δ 2.29 (s, 3 H), 2.45 (s, 3 H), 5.62 (s, 1 H), 7.15 (d, 1 H), 7.33 (t, 2 H), 7.49 (t, 2 H), 7.95 (NH); MS 235 (M^+, 10), 193 (M − 42, 3l), 151 (M − 42 − 42, 53), 43 (100); HR-MS calcd 235.08449, found 235.0854.

Reaction of 14 with Rh_2OAc_4. A 20-mL solution of benzene containing 140 mg of **14** was heated until approximately 7 mL had distilled. Rh_2OAc_4 (approximately 15 mg) was added and the solution was refluxed for 6 h. The crude product obtained

after evaporation of the solvent was purified by two passes through a Chromatatron silica gel plate, using first 4:1 hexane–ethyl acetate and then 10:1 CH_2Cl_2–hexane. The yield of **15** was 16 mg (12%): ^1H NMR δ 1.19 (t, J = 7.1 Hz, 3 H), 3.34 (s, 3 H), 3.89 (d, J = 8.7 Hz, 1 H), 4.06 (m, 2 H), 4.58 (d, J = 8.7 Hz, 1 H, exchanged with D_2O), 7.2–7.5 (m, 5 H); ^{13}C NMR δ 14.0, 38.2, 62.0, 69.2, 127.7, 128.6, 129.8, 141.6, 168.1, 170.0; MS 237 (M^+, 10), 164 (M – CO_2Et, 16), 134 (M – CH(OH)CO_2Et, 100); HR-MS calcd 237.10015, found 237.0961.

Registry No. **3a**, 38118-69-3; **3b**, 124069-95-0; **3c**, 38118-73-9; **3d**, 124069-96-1; **3e**, 124069-97-2; **4a**, 124043-91-0; **4b**, 124070-01-5; **4c**, 124070-02-6; **4d**, 124070-03-7; **4e**, 124070-04-8; **9**, 124069-98-3; **10**, 124070-05-9; **11**, 22760-66-3; **12**, 124070-06-0; **14**, 124069-99-4; **15**, 124070-00-4; PhNHMe, 100-61-8; PhNHPh, 122-39-4; *m*-$ClC_6H_4NHCH_2Ph$, 50798-95-3; *m*-$NO_2C_6H_4NHCH_2Ph$, 33334-94-0; $PhNH_2$, 62-53-3; *p*-$MeC_6H_4SO_2N_3$, 941-55-9; Rh_2OAc_4, 15956-28-2; *N*,2-dimethyl-4-methoxyaniline, 86735-53-7; 1,2,3,4-tetrahydroquinoline, 635-46-1; diketene, 674-82-8.

Synthesis of (±)-Frullanolide: An Application of Radical Closure

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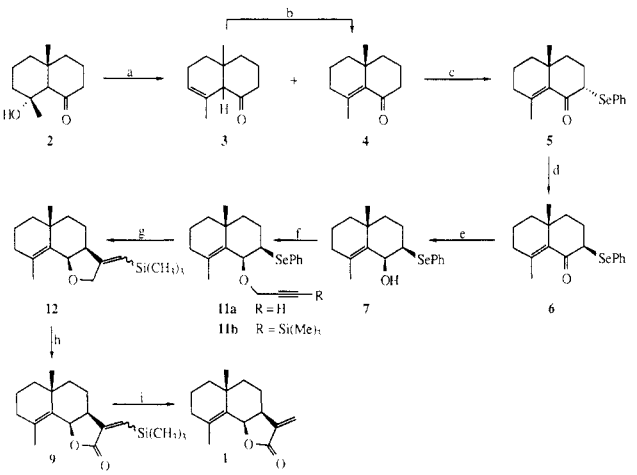
The sesquiterpene, frullanolide (**1**), is an allergy-producing substance that occurs in certain plants of the *Frullania* genus.[1] Several syntheses of this compound have been described;[2] we report here a new route in which radical cyclization is the essential step for constructing the α-methylene γ-lactone unit.

The bicyclic ketone **4** (Scheme I) is a known compound,[3] and its carbon skeleton represents a substructure of frullanolide. We sought, therefore, to develop a method, applicable to ketone **4**, for generating the γ-lactone[4] of the natural product.

A mixture of the isomeric ketones **3** and **4** was prepared along the lines described in the literature via the racemic tertiary alcohol **2**.[3] We used *p*-toluenesulfonic acid for catalytic dehydration of the intermediate tertiary alcohol **2** and, in contrast to the reported[3] use of thionyl chloride, this procedure gives the conjugated isomer **4** as the major product. The two ketones are separable by flash chromatography, and the minor component **3** can be isomerized to the desired ketone **4** by the action of rhodium trichloride trihydrate, optimally, in 2:8 ethanol–benzene at reflux. The equilibration gives a mixture of **3** and **4** in a 1:2 ratio, and the required material can be isolated easily.

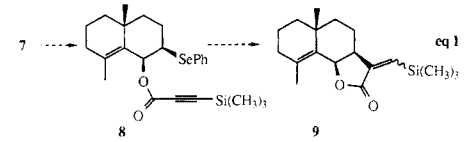
Kinetic deprotonation of **4**, and treatment of the enolate with phenylselenenyl chloride, affords the α-(phenylseleno) ketone **5**. When this, in turn, is deprotonated and reprotonated with saturated aqueous ammonium chloride, it is converted into the β-isomer **6**, which has the phenylseleno group in the equatorial conformation required for the next step. This involves reduction of the carbonyl so as to generate alcohol **7**. Reduction of α-(phenylseleno) ketones is known[5] to present difficulties as there is a tendency for the phenylseleno group to be lost and, of several common hydride reducing agents that we examined, only diisobutylaluminum hydride was effective.[5]

Scheme I[a]



[a] (a) 76% from 3-(4-oxopentyl)-2-cyclohexen-1-one; (b) $RhCl_3 \cdot 3H_2O$; (c) LDA; PhSeCl; 82%; (d) LDA; NH_4Cl; 71% from **4**; (e) DIBAL; 70%; (f) NaH; 3-bromo-1-(trimethylsilyl)-1-propyne; 69% of **11b**; (g) Ph_3SnH, AIBN; (h) CrO_3–pyridine; 52% from **11b**; (i) PhSH, Et_3N; Bu_4NF, methylacrylate; 68% from **9**.

We had intended to acylate the alcohol (**7** → **8**; eq 1) so that the synthesis could be completed by radical cyclization of the resulting ester (**8** → **9** → **1**; eq 1). Analogous clo-



sures of simple crotonic[6] and propiolic[7] esters are known, but the method could not be applied here because we were unable to acylate the hydroxyl group. We treated alcohol **7** in ether or dichloromethane with propiolic acid, DCC, and DMAP[8] but observed only loss of the phenylseleno group. 3-(Trimethylsilyl)-2-propynoic acid[9] and 3-(phenylthio)-2-propenoic acid[10] failed to react under similar conditions, or when the standard[11] procedure using 2-chloro-*N*-methylpyridinium iodide was applied.

We also examined the possibility of using (phenylseleno) alcohol **10** (eq 2), which was readily made by DIBAL reduction of **5**. However, application of the Mitsunobu reaction with 3-(trimethylsilyl)-2-propynoic acid or with 3-(phenylthio)-2-propenoic acid was not successful. The

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