fluorocarbene intermediate. When the insertion reaction was carried out in the presence of an excess of tetramethylethylene, the sole product was $C_6F_5CF_2CF_2Cu$; no difluorocyclopropane derivative was observed. We propose that CF_3Cu is in equilibrium with a copper difluorocarbenoid complex,[8] followed by insertion into the C–Cu bond of C_6F_5Cu to form $C_6F_5CF_2Cu$, which is more reactive toward insertion than C_6F_5Cu. Consequently, only the double insertion product was formed. When the stoichiometry of C_6F_5Cu and CF_3Cu was 1:1, $C_6F_5CF_2CF_2Cu$ was formed in 55% yield and 45% of C_6F_5Cu remained. In the case of the addition of pregenerated $C_6F_5CF_2CdX$[9] to a solution of CF_3CdX in the presence of CuBr, $C_6F_5CF_2CF_2Cu$[10] was observed by ^{19}F NMR analysis.

$$CF_3Cu \rightleftharpoons CF_2{=}CuF$$

$$C_6F_5Cu + CF_2{=}CuF \xrightarrow{\text{slow}} C_6F_5CF_2Cu$$

$$C_6F_5CF_2Cu + CF_2{=}CuF \xrightarrow{\text{fast}} C_6F_5CF_2CF_2Cu$$

$C_6F_5CF_2CF_2Cu$ exhibits good thermal stability from room temperature to 55 °C. At higher temperatures (>85 °C) it undergoes decomposition.

Typical reactions of the (perfluoro-2-phenylethyl)copper reagent formed in situ are illustrated in Scheme I.

In conclusion, this work demonstrates that (trifluoromethyl)copper can be used for the insertion of CF_2 units into the carbon–copper bond of (pentafluorophenyl)copper and provides an unequivocal route to the (perfluoro-2-phenylethyl)copper reagent.[11] This reagent is also produced in high yield in situ from the (trifluoromethyl)cadmium or -zinc reagents and the (pentafluorophenyl)cadmium reagent in the presence of cuprous halide under mild conditions. Future work will focus on the applicability and generality of this novel difluoromethylene insertion process.

Acknowledgment. We thank the National Science Foundation for generous support of this work and Professor V. Platonov for a sample of $C_6F_5CF_2Br$.

Registry No. A, 140468-37-7; B, 140468-38-8; $C_6F_5CF_2CF_2Br$, 140468-34-4; C_6F_5CdBr, 104698-12-6; CF_3ZnBr, 97571-13-6; $C_6F_5CF_2CF_2Cu$, 140468-35-5; $C_6F_5CF_2CF_2SO_2Cu$, 140468-36-6; CF_3CdBr, 97571-11-4; $C_6F_5CF_2CF_2CH_2CH{=}CH_2$, 140468-39-9; $ClCH_2CH{=}C(CH_3)_2$, 503-60-6; $C_6F_5CF_2CF_2CH_2CH{=}C(CH_3)_2$, 140468-40-2; $C_6F_5CF_2CF_2CH{=}CHC_6H_5$, 140468-41-3; $C_6H_5CH{=}CHBr$, 103-64-0; m-$CH_3C_6H_4CF_2CF_2C_6F_5$, 140468-42-4; m-$CH_3C_6H_4I$, 625-95-6; o-$NO_2C_6H_4CF_2CF_2C_6F_5$, 140468-43-5; o-$NO_2C_6H_4I$, 609-73-4; $C_6F_5CF_2Br$, 35523-39-8; $C_6F_5CF_2Cu$, 140468-44-6; $C_6F_5CF_2CdCF_2C_6F_5$, 140468-45-7; $C_6F_5CF_2CdBr$, 140468-46-8.

(8) Transition metal trifluoromethyl complexes (CF_3–M) exhibit strong M–C and weak C–F bonds. Clark and Tsai have proposed a hyperconjugation argument that employs "no-bond" resonance structures $(M{=}CF_2)^+F^-$. See: Clark, H. C.; Tsai, J. H. *J. Organomet. Chem.* **1967**, *7*, 515. Also see: Cotton, F. A.; McCleverty, J. A. *J. Organomet. Chem.* **1965**, *4*, 490. Cotton, F. A.; Wing, R. M. *J. Organomet. Chem.* **1967**, *9*, 511. Lichtenberger, D. L.; Fenske, R. F. *Inorg. Chem.* **1974**, *13*, 486. Hall, M. B.; Fenske, R. F. *Inorg. Chem.* **1972**, *11*, 768. Brothers, P. J.; Roper, W. R. *Chem. Rev.* **1988**, *88*, 1293.

(9) $C_6F_5CF_2CdX$ could be readily prepared from the reaction of $C_6F_5CF_2Br$ and cadmium in DMF at room temperature. Metathesis of the cadmium reagent with CuBr at −35 °C gave a (perfluorobenzyl)copper reagent. ^{19}F NMR (DMF, vs $C_6H_5CF_3$) indicated two species of the copper reagent in a 7:1 ratio: **A**, −24.1 (t, J = 22.0 Hz, 2 F), −82.8 (m, 2 F), −97.7 (m, 1 F), −102.4 (m, 2 F); **B**, −28.0 (t, J = 22.0 Hz, 2 F), −82.8 (m, 2 F), −97.7 (m, 1 F), −102.4 (m, 2 F). Addition of allyl bromide to the copper reagent solution caused the disappearance of both species and resulted in the formation of $C_6F_5CF_2CH_2CH{=}CH_2$.

(10) The enhanced reactivity of $C_6F_5CF_2Cu$ relative to C_6F_5Cu correlates with the stability of these reagents. $C_6F_5CF_2Cu$ decomposes readily at room temperature, whereas C_6F_5Cu is stable indefinitely at room temperature.

(11) The insertion process is not specific for C_6F_5Cu. Other fluorinated copper reagents exhibit similar behavior. Preliminary work with p-XC_6F_4Cu (X = H, CH_3O) yields p-$XC_6F_4CF_2CF_2Cu$. Similarly, $\overline{C_2F_2NC_2F_2C}Cu$ gives $\overline{C_2F_2NC_2F_2CCF_2CF_2Cu}$ and (Z)-$CF_3CF{=}CFCu$ gives (E)-$CF_3CF{=}CFCF_2CF_2Cu$ under similar conditions. In related work,[12] $(EtO)_2P(O)CF_2Cu$ inserted CF_2 to produce $(EtO)_2P(O)CF_2CF_2Cu$.

(12) Work in progress with H. K. Nair.

Supplementary Material Available: Experimental procedures, characterization data, and NMR spectra for all compounds described in Scheme I, as well as ^{19}F NMR spectra of $C_6F_5CF_2CdX$ (X = Br, $CF_2C_6F_5$), $C_6F_5CF_2Cu$, and $C_6F_5CF_2CF_2Cu$ and ^{113}Cd NMR spectra of $C_6F_5CF_2CdX$ (X = Br, $CF_2C_6F_5$) (55 pages). Ordering information is given on any current masthead page.

Synthesis of Strychnine via the Wieland–Gumlich Aldehyde

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The synthesis of strychnine (**1**) by Woodward[1] not only confirmed its structure but also was the first total synthesis of a complicated natural product. Considering the extensive synthetic efforts devoted to indole alkaloids, the original Woodward report (1953) still stands as the only synthesis of strychnine.[2]

As part of our studies on the synthesis of heptacyclic indole alkaloids,[3] we report the synthesis of the hexacyclic relay compound **2**, Scheme I, which has been correlated by degradation of strychnine, and its conversion into strychnine.

The tetracyclic amine **3**[4] (Scheme II) was treated with β,β,β-trichloroethyl chloroformate to give a mixture of **4** (38%) and **5** (25%). Exposure of **4** to NaOMe/MeOH gave **5** (62% from **3**). Protection of the indole nitrogen and reductive removal of the β,β,β-trichloroethyl carbamate (Zn/AcOH/THF) gave the secondary amine **7**. Acetylation of **7** with $PhSCH_2CO_2H$/BOPCl gave the amide **8**, which was directly oxidized to the diastereomeric sulfoxides **9**. Treatment of **9** with NaH/THF resulted in intramolecular conjugate addition to give the tetracyclic lactam **10** (as a mixture of stereoisomers at the C–S and S–O bonds). Similarly the sulfide **8** gave the corresponding tetracyclic lactam sulfide **10a** (X-ray). The mixture of sulfoxides **10** was subjected to Pummerer-type conditions followed by mercuric ion assisted hydrolysis to give the dione **11** as a single stereoisomer which exists in

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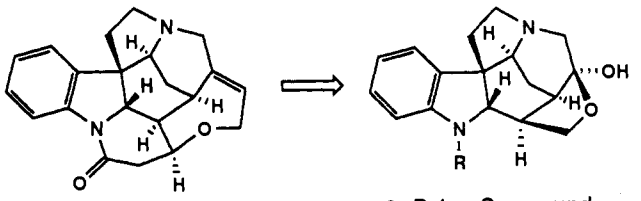
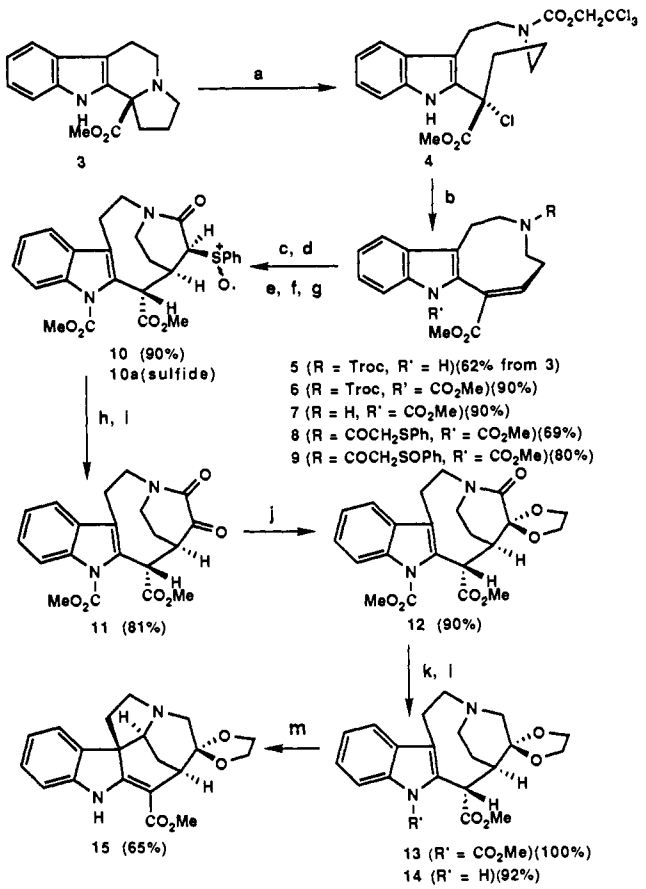
Scheme I



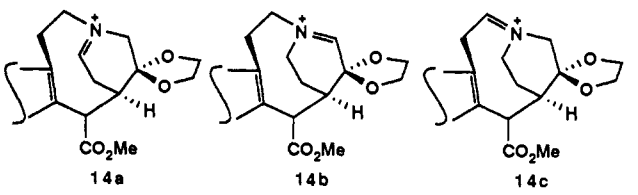
Scheme II[a]



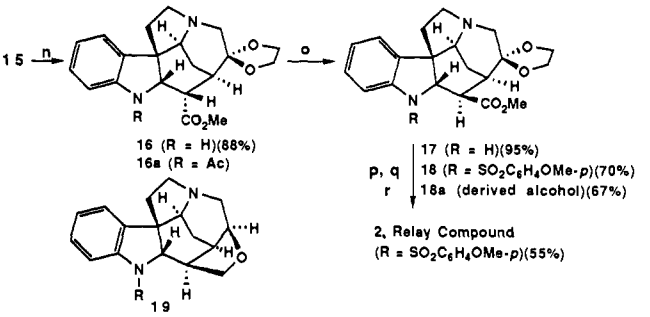
[a](a) TrocCl/CH_2Cl_2, **4** (38%)/**5** (25%). (b) NaOMe/MeOH, **5** (98%). (c) 50% aqueous NaOH/CH_2Cl_2/$ClCO_2Me$, PTC (90%). (d) Zn/AcOH/THF (90%). (e) $PhSCH_2CO_2H$/BOPCl/Et_3N/CH_2Cl_2 (69%). (f) MCPBA/CH_2Cl_2/0 °C (80%). (g) NaH/THF (90%). (h) TFAA/2,6-di-*tert*-butyl-4-methylpyridine. (i) HgO/$CdCO_3$/THF, H_2O (81% from **10**). (j) $BrCH_2CH_2OH$/DBU/toluene (90%). (k) BH_3·THF (100%). (l) Na_2CO_3/MeOH reflux (92%). (m) $Hg(OAc)_2$/AcOH (65%).

equilibrium with its ketone hydrate. The ketal **12** could be readily formed by treatment of **11** with $BrCH_2CH_2OH$/DBU/toluene.[5] Reduction of **12** with BH_3·THF gave **13**, which was hydrolyzed to the unprotected indole **14**. Remarkably, during purification by chromatography (SiO_2) **14** was partially converted into the cyclized product **15**! Dehydrogenation of the tertiary amine functionality in **14** can, in principle, give rise to the three iminium ions **14a–c**, Scheme III. The desired iminium ion **14a** is the least strained and is endocyclic to both six- and nine-membered rings. In a more controlled fashion, treatment of **14** with $Hg(OAc)_2$/AcOH/25 °C gave **15**, along with small amounts of the cyclized product from **14b** and an aryl mercurated derivative of **15** which upon reduction ($NaBH_4$) gave **15**.[6]

Scheme III

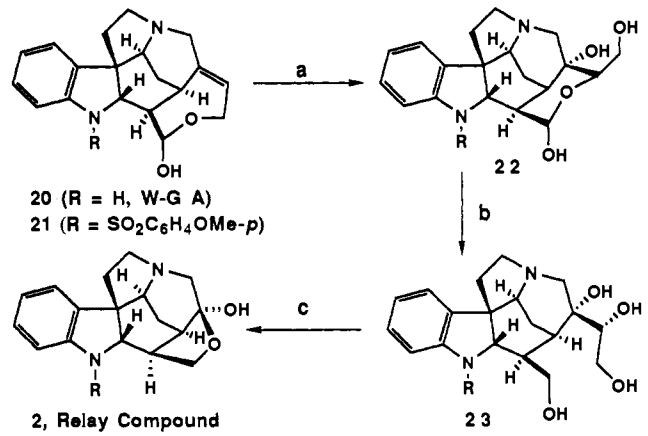


Scheme IV[a]



[a](n) Zn/H_2SO_4/MeOH (88%). (o) MeONa/MeOH (95%). (p) *p*-$MeOC_6H_4SO_2Cl$/EtN^iPr_2/DMAP/CH_2Cl_2 (70%). (q) $LiBH_4$/THF/$HN(CH_2CH_2OH)_2$ (67%). (r) $HClO_4$ (55%).

Scheme V[a,b]



[a]R = $SO_2C_6H_4OMe$-*p*. [b](a) OsO_4 (cat.)/*N*-methylmorpholine *N*-oxide/THF-^{t}BuOH-H_2O (70–80%). (b) $LiBH_4$/THF (43–56%). (c) H_5IO_6/CF_3CO_2H-MeOH-H_2O (55–61%).

We have made both antipodal forms of **11** by coupling **7** with (+)-*p*-$CH_3C_6H_4S(O)CH_2CO_2H$, separating the four diastereomers of the cyclized sulfoxide analogue of **10**, combining the pairs with the same absolute configuration (ORD/CD), and conversion into **11**.

The β-aminoacrylate **15** was reduced to the saturated ester **16** by treatment with Zn/H_2SO_4/MeOH, Scheme IV. The stereochemistry of **16** (α-CO_2Me) was evident from the vicinal ^1H coupling of 4.5 Hz, and this was confirmed by X-ray crystal analysis of the *N*-acetyl derivative **16a**. Treatment of **16** with NaOMe/MeOH completely epimerized the ester to give **17** (vicinal ^1H coupling of 9.9 Hz), which was protected as the *p*-methoxybenzenesulfonamide derivative **18**. Reduction of **18** with $LiBH_4$/THF gave the corresponding alcohol **18a**, with a boron hydride moiety attached to the basic amine. Treatment of this compound with perchloric acid resulted in reduction of the deprotected carbonyl group and the formation of **19** (X-ray). Carrying out the $LiBH_4$ reduction followed by treatment with diethanolamine removed the boron hydride species, and then the

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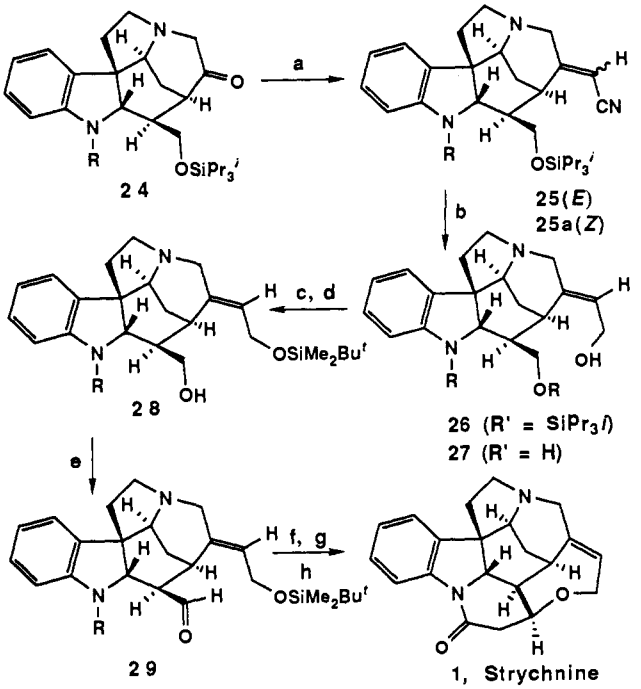
(6) This type of dehydrogenation has been used for the synthesis of *Aspidosperma* and *Strychnos* alkaloids. Camerman, A.; Camerman, N.; Kutney, J. P.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 637. Crawley, G. C.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1971**, 685.

Scheme VI[a,b]



[a] R = $SO_2C_6H_4OMe$-*p*. [b] (a) $(EtO)_2P(O)CH_2CN$/KHMDS/THF at 25 °C (72%). (b) DIBAL/CH_2Cl_2 H_3O^+ workup. $NaBH_4$/MeOH (31%). (c) 2 N HCl/MeOH (81%). (d) TBDMSOTf/DBU/CH_2Cl_2, -20 °C (60%). (e) SO_3·C_5H_5N/DMSO/Et_3N (70%). (f) py/HF (60%). (g) Na/anthracenide/DME (85%). (h) $CH_2(CO_2H)_2$/NaOAc/Ac_2O (70%).

ketal hydrolysis proceeded, as expected, to give the furanoside relay compound **2**.

At this stage we decided that **2** might be more readily available from degradation of strychnine (**1**), allowing examination of the final stages with substantially more material.[7]

The Wieland–Gumlich aldehyde (W-G A) **20**[8] was treated with *p*-$MeOC_6H_4SO_2Cl$/py (70%) followed by catalytic osmylation[9] to give the rearranged glycoside derivative **22** (70–80%) (X-ray). Reduction ($LiBH_4$) of **22** gave the tetrol **23** (43–56%), which was cleaved (H_5IO_6) to give the relay compound **2** (55–61%). Using this sequence **2** is available in gram quantities in three steps from **21**, Scheme V.

Treatment of **2** with TIPSOTf/DBU/CH_2Cl_2 from 0 °C to 25 °C gave the ketone **24** (69%). When **24** was treated with $(EtO)_2P(O)CH_2CN$/KHMDS/THF at 25 °C, it was cleanly transformed into **25** (72%) as a mixture of geometrical isomers, 3:2, with the desired *E* isomer in excess. The stereoisomers **25**/**25a** were readily separated, and the desired *E* isomer was reduced with DIBAL followed by $NaBH_4$ to give **26** (31% for two steps). The *Z* isomer could be converted into a mixture of the *E* and *Z* stereoisomers by irradiation (tungsten) in benzene. In this way we could obtain (*E*)-**25** in 52% yield after one cycle. Desilylation (2 N HCl/MeOH, 16 h) gave the diol **27** (81%), which was identical with the material made by DIBAL reduction (90%) of **21**. Selective protection of the allylic hydroxyl (TBDMSOTf/DBU/CH_2Cl_2/-20 °C) followed by oxidation (SO_3·C_5H_5N/DMSO/Et_3N) gave the aldehyde **29** (42% for two steps). Desilylation (py/HF) of **29** gave the protected W-G A **21** (60%), which was deprotected (Na/anthracenide)[10] to give **20** (85%). Since Robinson[11] has converted **20** into strychnine by treatment with $CH_2(CO_2H)_2$/NaOAc/Ac_2O (70%), this completes the second synthesis of strychnine, and the first of the W-G A, Scheme VI.

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Supplementary Material Available: Details of the X-ray structure determination of **10a**, **16a**, and **19**, including tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, and bond angles and spectral details for compounds **2**, **4–6**, **7a** (R = R' = H), **8–10**, **10a,b**, **11–13**, **15**, **16**, **16a**, **17**, **18**, **18a**, **19**, **21–25**, **25a**, and **26–29** (66 pages). Ordering information is given on any current masthead page.

(7) It is amusing to note that strychnine is less expensive than tryptamine!
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Enantioselectivity in FAB Mass Spectrometry

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Enantioselective complexation is a very important aspect of the field of molecular recognition. Modified crown ethers in particular have played fundamental roles as synthetic hosts in this field.[1] Cram and Lehn showed that chiral crown ethers involving 1,1-dinaphthyl units[2] or tartaric acid derivatives,[3] respectively, exhibited a high degree of enantioselectivity toward organic ammonium ions in solution. Many workers have continued to investigate enantiomeric selectivity with other types of modified crown compounds.[1,4-6] These selectivities are based upon different association constants, rate constants, calorimetric data, etc. To date, various detection methods of such diastereomeric complexes and their applications have been extensively developed with a variety of methods, such as NMR,[6,7] UV,[8] HPLC,[9] and others.[10] However, the application or the applicability of fast atom bombardment mass spectrometry (FABMS) to this has been virtually unknown.[11-14] We report here the first observation concerning

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