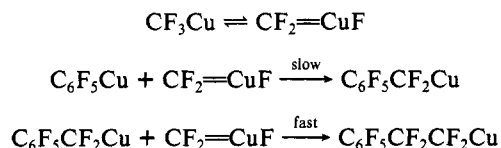


fluorocarbene intermediate. When the insertion reaction was carried out in the presence of an excess of tetramethylethylene, the sole product was $C_6F_5CF_2CF_2Cu$; no difluorocyclopropane derivative was observed. We propose that CF_3Cu is in equilibrium with a copper difluorocarbene complex,⁸ followed 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 ¹⁹F NMR analysis.



$C_6F_5CF_2CF_2Cu$ 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; $CICH_2CH=C(CH_3)_2$, 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. ¹⁹F 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_6H_4Cu ($X = H, CH_3O$) yields *p*- $XC_6H_4CF_2CF_2Cu$. Similarly, $C_2F_5NC_2F_5CCu$ gives $C_2F_5NC_2F_5CCF_2CF_2Cu$ 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 ¹⁹F NMR spectra of $C_6F_5CF_2CdX$ ($X = Br, CF_2C_6F_5$), $C_6F_5CF_2Cu$, and $C_6F_5CF_2CF_2Cu$ and ¹³Cd 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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Received February 6, 1992

The synthesis of strychnine (**1**) by Woodward¹ 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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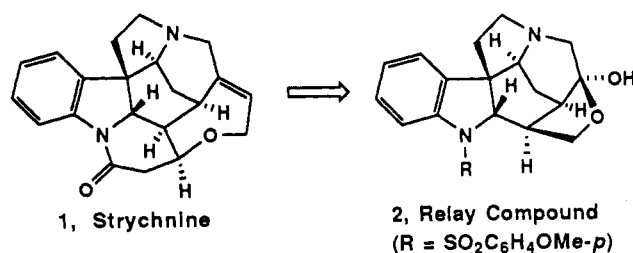
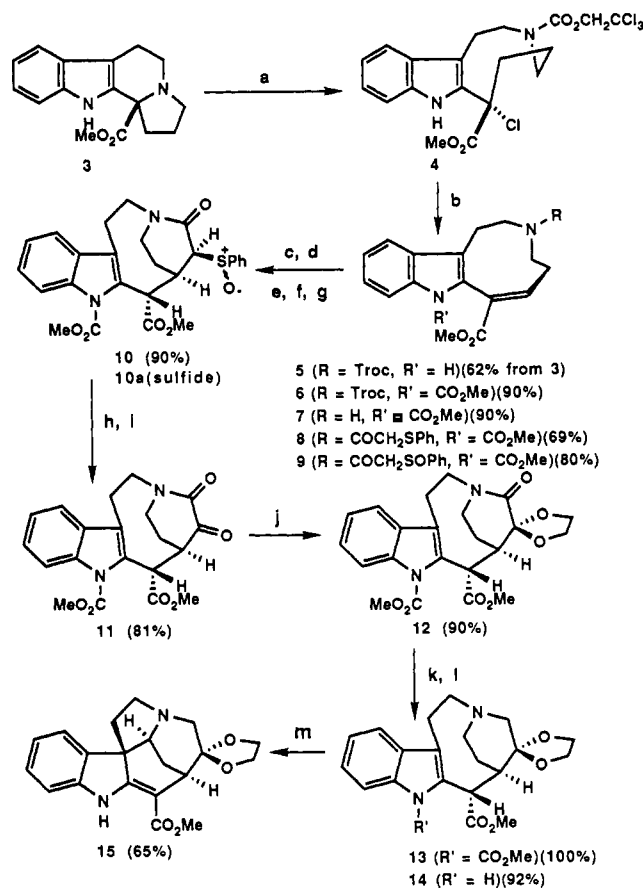
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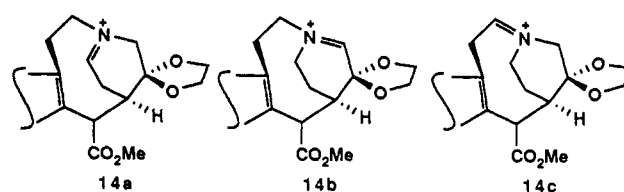
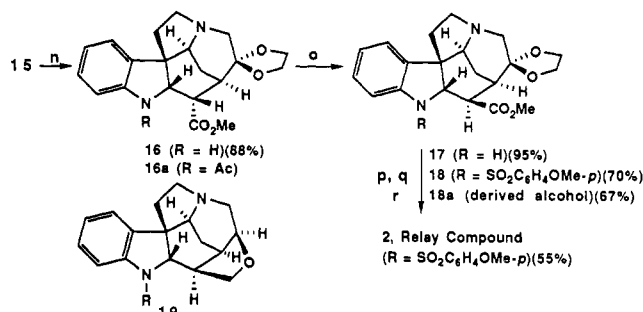
Scheme I

Scheme II^a

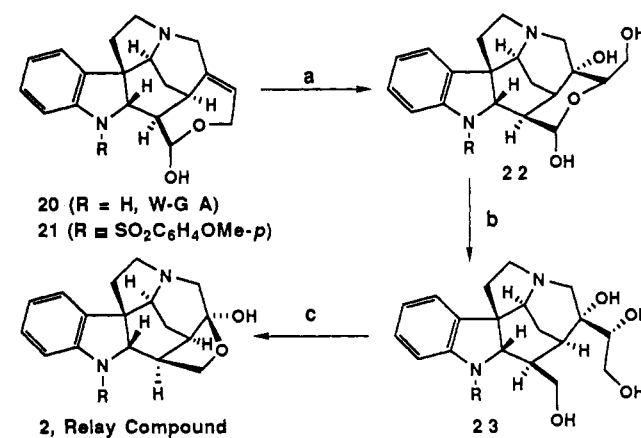
^a(a) TrocCl/CH₂Cl₂, 4 (38%)/5 (25%). (b) NaOMe/MeOH, 5 (98%). (c) 50% aqueous NaOH/CH₂Cl₂/ClCO₂Me, PTC (90%). (d) Zn/AcOH/THF (90%). (e) PhSCH₂CO₂H/BOPCl/Et₃N/CH₂Cl₂ (69%). (f) MCPBA/CH₂Cl₂/0 °C (80%). (g) NaH/THF (90%). (h) TFAA/2,6-di-*tert*-butyl-4-methylpyridine. (i) HgO/CdCO₃/THF, H₂O (81% from 10). (j) BrCH₂CH₂OH/DBU/toluene (90%). (k) BH₃/THF (100%). (l) Na₂CO₃/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 BrCH₂CH₂OH/DBU/toluene.⁵ Reduction of 12 with BH₃/THF gave 13, which was hydrolyzed to the unprotected indole 14. Remarkably, during purification by chromatography (SiO₂) 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 (NaBH₄) gave 15.⁶

Scheme III

Scheme IV^a

^a(n) Zn/H₂SO₄/MeOH (88%). (o) MeONa/MeOH (95%). (p) *p*-MeOC₆H₄SO₂Cl/Et₃N/Pr₂/DMAP/CH₂Cl₂ (70%). (q) LiBH₄/THF/HN(CH₂CH₂OH)₂ (67%). (r) HClO₄ (55%).

Scheme V^{a,b}

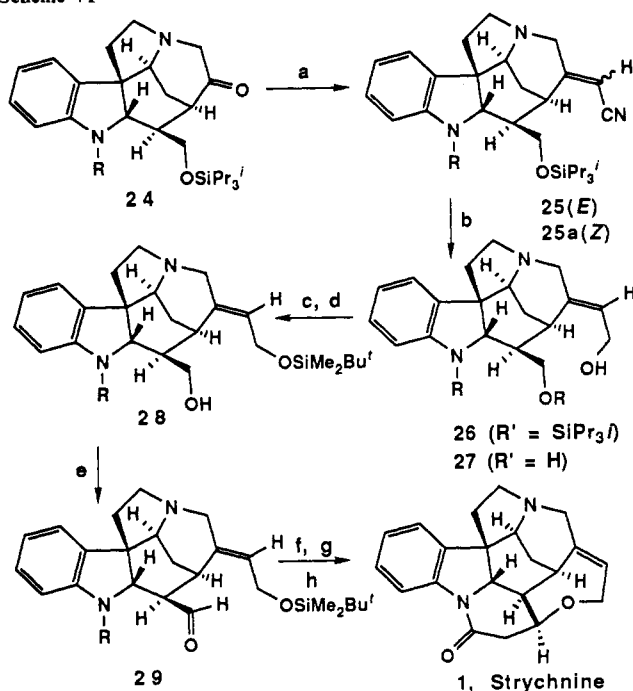
^aR = SO₂C₆H₄OMe-*p*. ^b(a) OsO₄ (cat.)/*N*-methylmorpholine *N*-oxide/THF–*t*-BuOH–H₂O (70–80%). (b) LiBH₄/THF (43–56%). (c) H₅IO₆/CF₃CO₂H–MeOH–H₂O (55–61%).

We have made both antipodal forms of 11 by coupling 7 with (+)-*p*-CH₃C₆H₄S(O)CH₂CO₂H, 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/H₂SO₄/MeOH, Scheme IV. The stereochemistry of 16 (α-CO₂Me) 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 LiBH₄/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 LiBH₄ reduction followed by treatment with diethanolamine removed the boron hydride species, and then the

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Scheme VI^{a,b}

^a R = SO₂C₆H₄OMe-*p*. ^b (a) (EtO)₂P(O)CH₂CN/KHMDS/THF at 25 °C (72%). (b) DIBAL/CH₂Cl₂ H₃O⁺ workup. NaBH₄/MeOH (31%). (c) 2 N HCl/MeOH (81%). (d) TBDMSOTf/DBU/CH₂Cl₂, -20 °C (60%). (e) SO₃-C₆H₄N/DMSO/Et₃N (70%). (f) py/HF (60%). (g) Na/anthracene/DME (85%). (h) CH₂(CO₂H)₂/NaOAc/Ac₂O (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*-MeOC₆H₄SO₂Cl/py (70%) followed by catalytic osmylation⁹ to give the rearranged glycoside derivative **22** (70–80%) (X-ray). Reduction (LiBH₄) of **22** gave the tetrol **23** (43–56%), which was cleaved (H₂IO₆) 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/CH₂Cl₂ from 0 °C to 25 °C gave the ketone **24** (69%). When **24** was treated with (EtO)₂P(O)CH₂CN/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 NaBH₄ 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/CH₂Cl₂; -20 °C) followed by oxidation (SO₃-C₆H₄N/DMSO/Et₃N) 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/anthracene)¹⁰ to give **20** (85%).

(7) It is amusing to note that strychnine is less expensive than tryptamine!

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Since Robinson¹¹ has converted **20** into strychnine by treatment with CH₂(CO₂H)₂/NaOAc/Ac₂O (70%), this completes the second synthesis of strychnine, and the first of the W-G A, Scheme VI.

Acknowledgment. The National Institutes of Health (GM 32718) are thanked for their financial support of this research. Dr. John C. Huffman (Molecular Structure Center, Indiana University, Bloomington, IN 47415) and Dr. Vince Lynch (UT, Austin) are thanked for the X-ray structure determination of compounds **10a**, **16a**, **19**, and **22**, respectively. L.M. thanks the Fulbright Commission for a fellowship.

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.

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Enantioselectivity in FAB Mass Spectrometry

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Received July 1, 1991

Revised Manuscript Received January 7, 1992

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 units² 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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