dissolved in heptane at 20 °C was added dropwise a heptane solution of 1.0–10.0 mmol of the alcohol (equimolar with the i-$Bu_3Al$). The solution was stirred for 1 h, during which time the isobutane gas was evolved.

The resulting solution was treated in two ways: (1) with the alkoxides of **8a** and **8b**, it was heated with 1.1 molar equiv of $AlBr_3$ and 0.05 equiv of $Cp_2TiCl_2$ for 24 h and worked up as with the ketone reductions and (2) with the alkoxide of **8c**, it was subjected successively to 1.1 mmol of $AlBr_3$ at reflux for 12 h and to 1.1 mmol of i-$Bu_2AlH$ and 0.02 molar equiv of $Ni(acac)_2$ for 6 h, followed by the usual workup.

**Acknowledgment.** The research was supported by Texas Alkyls Inc. of Deer Park, TX, whose fostering of research on synthetic applications for organoaluminum reagents has been most appreciated. Professor Guo-Xiu Zheng, visiting scientist at SUNY-Binghamton from the Institute of Chemistry, Academia Sinica, PRC, has been most helpful in optimizing the three-step reduction of dialkyl ketones to alkanes.

**Registry No.** **3b**, 45095-66-7; **6a**, 119-61-9; **6b**, 98-86-2; **6c**, 502-56-7; **8a**, 91-01-0; **8b**, 98-85-1; **8c**, 623-93-8; **9a**, 101-81-5; **9b**, 100-41-4; **9c**, 111-84-2; **10b**, 495-45-4; **12**, 35467-39-1; *i*-$Bu_2AlH$, 1191-15-7; *i*-$BuAlCl_2$, 1888-87-5; $AlBr_3$, 7727-15-3; $C_9H_{19}OH$, 143-08-8; *p*-$MeC_6H_4OH$, 106-44-5; *i*-$Bu_3Al$, 100-99-2; nonene, 27215-95-8; nickel(II) acetylacetonate, 3264-82-2; titanocene dichloride, 1271-19-8.

# Alkyne Reactions with the Cyclopalladated 8-Methylquinoline Ligand: Synthesis of Novel Heterocyclic Compounds with a Bridgehead Nitrogen[1]

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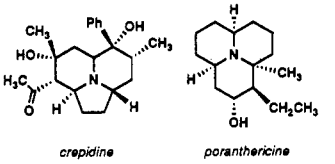
The stepwise reaction of cyclopalladated 8-methylquinoline (compound 1, obtained via intramolecular metalation of 8-methylquinoline by Pd(II)) with 2 equiv of various internal alkynes affords 4*H*-indolo[2,1,7-*cde*]quinolizines **3** through simultaneous Pd-mediated C–C and C–N bond formation. This reaction displays a high selectivity provided that the first alkyne reacting with 1 bears two electron-withdrawing substituents such as $-CF_3$ or $-CO_2Me$ and that the second alkyne is also substituted by electrophilic substituents. Varying the reaction conditions allowed us to isolate organometallic intermediates, whose nature shed some light upon the mechanism of the formation of **3**. Several deviations from the synthesis of **3** were encountered when different alkynes were reacted with **1**, e.g., with ethyl-3-phenylpropynoate a four-substituted α-pyrone was synthesized through C–O activation of one of the ester functions.

## Introduction

The indolizine (pyrrolo[1,2-*a*]pyridine) and quinolizine (pyrido[1,2-*a*]pyridine) nuclei are present in a large number of alkaloids. These bicyclic ring systems have been extensively studied not only for their use as drugs[2] but also by virtue of their applications in photographic processes[3] and as dyestuffs.[4] Naturally occurring derivatives include perhydroindolizine (indolizidine) and octahydroquinolizine (quinolizidine), trivially known as the alkaloids δ-coniceine and norlupinane, respectively. These fragments have been observed in several biologically active alkaloids such as (the

**Chart I**




(1) Reactivity of cyclopalladated compounds. 28. Part 27: Sutter, J. P.; Pfeffer, M.; De Cian, A.; Fischer, J. *Organometallics* **1992**, *11*, 386.

(2) (a) Dunn, M. A.; Maragoudakis, M. E.; Hait, P. K. *Biochim. Biophys. Acta* **1978**, 538, 328. (b) Maragoudakis, M. E.; Kalinsky, H. J.; Wasvary, J. *J. Pharmacol. Exp. Ther.* **1978**, *204*, 372. (c) Alaimo, R. J.; Hatton, C. J.; Eckmann, M. K. *J. Med. Chem.* **1970**, *13*, 554. (d) Alaimo, R. J.; Goldenberg, M. M. *J. Med. Chem.* **1975**, *18*, 1145. (e) Goldenberg, M. M.; Ilse, A. C. *Arch. Int. Pharmacodyn. Ther.* **1977**, *228*, 150. (f) Alaimo, R. J.; Goldenberg, M. M. *J. Pharm. Sci.* **1978**, *67*, 1183. (g) Thomas, J. *J. Med. Chem.* **1963**, *6*, 456. (h) Thyagarajan, M. *Chem. Rev.* **1954**, *54*, 1019. (i) Leonard, N. J. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 3, p 120; Vol. 7, p 254. (j) Henry, T. A. In *The Plant Alkaloids*; Blakiston: Philadelphia, 1949; pp 116–153 and 661–672. (k) Mosby, W. L. *Chem. Heterocycl. Compd.* **1961**, *15*, 1046.

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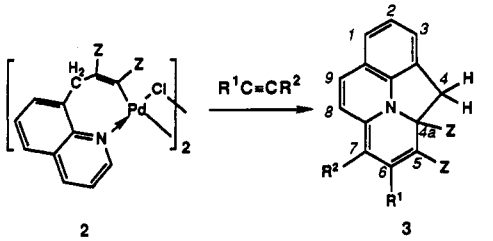
**Table I. Synthesis of [2.3.3]Cyclazines from 2 and Alkynes**




2 3

| entry | compd | Z | $R^1$ | $R^2$ | reaction cond | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | $CO_2Me$ | $CO_2Me$ | $CO_2Me$ | PhCl, 100 °C, 0.5 h | 91[a] |
| 2 | **3b** | $CO_2Me$ | Ph | Ph | $C_2H_4Cl_2$, reflux, 15 h | 52[a] |
| 3 | **3c** | $CO_2Me$ | $CO_2Et$ | Ph | $C_2H_4Cl_2$, reflux, 18 h | 55[a] |
| 4 | **3d** | $CO_2Me$ | $CO_2Et$ | Me | $C_2H_4Cl_2$, reflux, 18 h | 9[a] |
| 5 | **3e** | $CO_2Me$ | $CO_2Me$ | Ph | $C_2H_4Cl_2$, reflux, 14 h | 64[a] |
| 6 | **3f, 3g** | $CO_2Me$ | *p*-$C_6H_4NO_2$ | Ph | $C_2H_4Cl_2$, reflux, 10 h | 22[a] |
| | **3g, 3f** | $CO_2Me$ | Ph | *p*-$C_6H_4NO_2$ | | 20[a] |
| 7 | **3h, 3i** | $CO_2Me$ | *m*-$C_6H_4CF_3$ | Ph | $C_2H_4Cl_2$, reflux, 15 h | 36[a] |
| | **3i, 3h** | $CO_2Me$ | Ph | *m*-$C_6H_4CF_3$ | | 19[a] |
| 8 | **3j** | $CO_2Me$ | Ph | *p*-$C_6H_4CH_3$ | $C_2H_4Cl_2$, reflux, 20 h | traces[b] |
| 9 | **3k** | $CO_2Me$ | Ph | *p*-$C_6H_4OCH_3$ | $C_2H_4Cl_2$, reflux, 11 h | traces[b] |
| 10 | **3l** | $CF_3$ | $CO_2Me$ | $CO_2Me$ | PhCl, 100 °C, 6 h | 58[a] |
| 11 | **3m** | $CF_3$ | Ph | Ph | PhCl, 100 °C, 7 h | 50[b] |
| 12 | **3n**[c] | $CF_3$ | $CO_2Et$ | Ph | PhCl, 110 °C, 2 h | 70[b] |
| | **3o**[c] | $CF_3$ | Ph | $CO_2Et$ | | 8[b] |
| 13 | **3p**[c] | $CF_3$ | $CO_2Me$ | Ph | PhCl, 110 °C, 2 h | 44,[b] 11[d] |
| | **3q**[c] | $CF_3$ | Ph | $CO_2Me$ | | 22[b] |

[a] Isolated yield after chromatography on alumina. [b] Yield determined by $^1H$ NMR. [c] See ref 17 for the assignment of the regioisomers. [d] Yield after crystallization.

cyclazidine derivatives) crepidine and porantherine.[5,6]

One possible synthetic strategy aimed at the synthesis of related heterocyclic nuclei might involve the reduction of the corresponding unsaturated species [2.3.3]- and [3.3.3]cyclazines,[7] respectively. Whereas several routes are available for the obtainment of the latter heterocycles, synthetic pathways toward the [2.3.3]cyclazines are still scarce.[8] The synthesis of pyrrolo[2,1,5-*de*]quinolizines was first described by Acheson and Feinberg by heating 2-styrylpyridine and dimethylacetylene dicarboxylate.[9] This method is the only one reported prior to our work in which the five- and six-membered rings are formed simultaneously. This is in contrast to other methods which require in most cases a pre-formed indolizine or quinolizine skeleton.[10,11] However, Acheson and Feinberg's preparation proved to be somewhat limited in scope since it was only successful for the reaction with the one specific alkyne.

We have reported recently in a preliminary communication the synthesis of a series of tetrasubstituted [2.3.3]cyclazine derivatives **3** (in reasonable to good yields) from the reaction of cyclopalladated 8-methylquinoline **1** with internal alkynes.[12] Compounds **3**, which can be described appropriately as 4*H*-indolo[2,1,7-*cde*]-quinolizines, are novel examples in the [2.3.3]cyclazine series and are unprecedented members of the indoloquinolizine family to which, inter alia, also belong the yohimbine alkaloids and their derivatives.[13]

We describe herein full details of the synthesis and characterization of this series of [2.3.3]cyclazines in which a variety of substituents can be introduced at the 4a, 5, 6, and 7 positions. Some deviation reactions affording functionalized pyrones or olefins dependent mainly upon the nature of the alkyne substituents will also be described.

## Results

Via a slight modification of the procedure reported by Deeming, bis(μ-chloro)bis(8-quinolylmethyl-*C*,*N*)dipalladium(II), **1**, was obtained in high yield from 8-methylquinoline (8-mq) and palladium acetate, followed by reaction with LiCl.[14] Reaction of **1** with 1 equiv of dimethylacetylene dicarboxylate (DMAD) per palladium atom[15a] or with excess hexafluorobut-2-yne (HFB)[15b] led

(5) (a) Kierkegaard, P.; Pilotti, A. M.; Leander, K. *Acta Chem. Scand.* **1970**, *24*, 3757. (b) Pilloti, A. M. *Acta. Crystallogr. Part B* **1971**, *27*, 887.

(6) Denne, W. A.; Mcl. Mathieson, A. *J. Cryst. Mol. Struct.* **1973**, *3*, 139.

(7) Windgassen, R. J., Jr.; Saunders, W. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1959**, *81*, 1459. The word *cyclazine* refers to the general case of a conjugate unsaturated cycle, held planar by three covalent bonds to an internal nitrogen atom. The individual members can be distinguished by placing in brackets numerals corresponding to the number of atoms on the peripheral cycle between points of bonding to the internal nitrogen; consequently, the example shown below is a 2*H*-[2.3.3]cyclazine. The generally accepted cyclazine nomenclature, as proposed by Leaver, and which is adopted in this paper, involves placing the bracketed numerals in increasing number before the word *cyclazine* rather than in the middle.[10b]

(8) (a) Matsumoto, K.; Uchida, T.; Yamagushi, J. *Yuki Gosei Kaguda Kyohaishi* **1977**, *35*, 739; *Chem. Abstr.* **1978**, *88*, 37642. (b) Flitsch, W.; Krämer, U. *Adv. Heterocycl. Chem.* **1978**, *22*, 321. (c) Taurins, A. *Chem. Heterocycl. Compd.* **1977**, *30*, 245. (d) Farquhar, D.; Gough, T. T.; Leaver, D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 341. (e) Kanemasa, S.; Kobira, S.; Kajigaeshi, J. *Heterocycles* **1980**, *14*, 1107.

(9) (a) Acheson, R. M.; Feinberg, R. S. *J. Chem. Soc., Chem. Commun.* **1965**, 342. (b) Acheson, R. M.; Feinberg, R. S. *J. Chem. Soc. C* **1968**, 351.

(10) (a) Gibson, W. K.; Leaver, D.; Roff, J. E.; Cumming, C. W. *J. Chem. Soc., Chem. Commun.* **1967**, 214. (b) Dick, J. W.; Gibson, W. K.; Leaver, P.; Roff, J. E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3150.

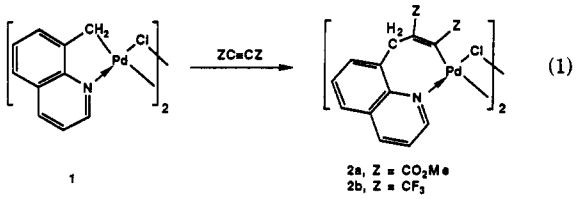
(11) (a) Ram, P. S.; Srinivasan, V. R. *Ind. J. Chem., Sect. B* **1977**, *15*, 1044. (b) Pschorr, R. *Ann.* **1912**, *391*, 40.

(12) Pfeffer, M.; Rotteveel, M. A. *Recl. Chem. Trav. Pays-Bas* **1989**, *108*, 317.

(13) (a) Stoll, A.; Hofmann, A. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, p 726. (b) Glasby, J. S. In *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975. (c) Boekelheide, V.; Prelog, K. Indole Alkaloids. In *Progress in Organic Chemistry*; Academic Press: New York, 1955; Vol. 3, p 218. (d) Smith, G. F. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, p 592.

(14) (a) Deeming, A. J.; Rothwell, I. P. *J. Organomet. Chem.* **1981**, *205*, 117. (b) Pfeffer, M. *Inorganic Synthesis*; Kaesz, H. D., Ed.; Wiley Interscience: New York, 1989; Vol. 26, p 211.

to the formation of the seven-membered palladocycles **2a** and **2b**, respectively.




Traces of **3a** were obtained during the preparation of **2a** even when less than 1 equiv of DMAD per Pd atom was employed.[15a] We have now found that reaction of **2a** with a second equivalent of DMAD in chlorobenzene at 100 °C gives **3a** in almost quantitative yield. When **2a** and **2b** were heated in the presence of disubstituted alkynes in either chlorobenzene at 100 °C or refluxing 1,2-dichloroethane, the reaction reached completion over a period of 0.5–18 h. The color changed from yellow to dark purple/red concurrent with formation of palladium metal, giving the cyclazines **3** in reasonable to good yields. The results are summarized in Table I. As can be seen from Table I, starting from compound **2**, which has to carry two strongly electronwithdrawing groups for reasons that will be discussed later, the synthesis of [2.3.3]cyclazines proceeds with diphenylacetylene (DPA) or with alkynes substituted by at least one electron-withdrawing group. The (isolated) yields for **3a–i** are better than for **3l–q** since the latter decompose on either alumina or silica supports during purification. For **3l–q** the $^1$H NMR spectra of the crude reaction products[16] showed a conversion up to ca. 78%. In order to obtain analytically pure samples the compounds were purified by fractional crystallization, resulting in considerable loss of product.

The $^1$H NMR spectrum of **3a** shows the presence of four nonequivalent carbomethoxy groups, the diastereotopic methylene protons, and another AB signal at low field which could be assigned to the protons at carbons 8 and 9 (see Table I). The structure of **3a** was furthermore unambiguously established by an X-ray analysis (see supplementary material for the structure), which is to our knowledge the first crystal structure determination of a [2.3.3]cyclazine. In compound **3a** one extremity of a $C_4(CO_2Me)_4$ unit bridges the nitrogen and the methylene group to give the five-membered ring. The other terminus of this C4 chain is bound to the carbon in an ortho position to the nitrogen of the former quinoline ring to form the new six-membered ring. Furthermore, the structure shows a central (bridgehead) nitrogen atom in a planar environment. The nitrogen lone pair probably participates in the highly conjugated $\pi$ system as is suggested by the fact that protonation is only possible with concentrated acid. This lack of basicity is not surprising since quaternarization of the nitrogen would require isolation of the central atom and consequent loss of resonance energy.[7] These data allow us to describe **3a** as a 4*H*-4a,5,6,7-tetracarbomethoxyindolo[2,1,7-*cde*]quinolizine.

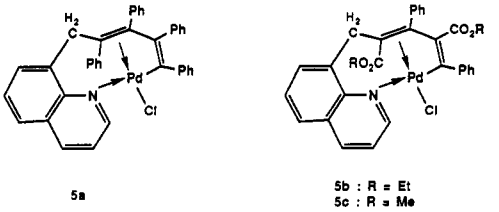
The interpretation of the $^1$H NMR spectra of **3b–n** is less straightforward than for **3a** since the methylene protons appear as a singlet even at low temperature for most of these compounds. For **3c** this is in contradiction with the fact that the $CH_2$ protons of the ethyl substituent appear as an $ABX_3$ type pattern. For **3n** the spectrum shows an AB type pattern for the quinoline $CH_2$ group and a quartet for the ethyl $CH_2$ group. The structure of **3c** was ascertained by X-ray diffraction studies (see supplementary material for the structure). The magnetical equivalence of the two quinoline $CH_2$ protons must therefore be purely coincidental.

It has been pointed out frequently that the insertion of alkynes into the Pd–C bonds of compounds related to **2** displays some degree of regioselectivity. This is also obviously the case for **3c** and **3d** for which the other regioisomer was not detectable in its crude $^1$H NMR spectrum. However, no selectivity was found for the other unsymmetrical alkynes used in this study. Noticeably, no selectivity was found for the diarylalkynes (entries 6 and 7), a result that emphazises the importance of the steric effects of the alkyne substituents upon the insertion of the alkyne into the Pd–C bond.[17]

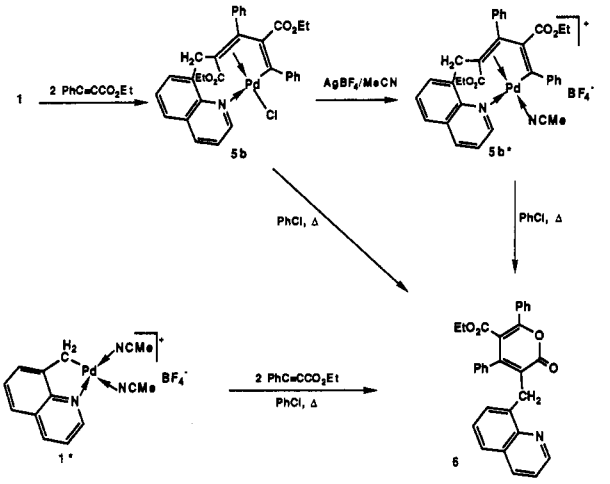
With but-2-yne, hex-3-yne, or 3,3-diethoxy-1-phenylprop-1-yne, no cyclazine formation was observed.[18]

The influence of the alkyne substituents is of paramount importance in determining which compound will result from the reaction of **1** with alkynes. It was previously shown that with DPA[15b] or ethyl-3-phenylpropynoate[15a]

**Chart II**




**Scheme I**




(15) (a) Pereira, M. T.; Pfeffer, M.; Rotteveel, M. A. *J. Organomet. Chem.* **1989**, *375*, 139. (b) Bahsoun, A.; Dehand, J.; Pfeffer, M.; Zinsius, M.; Bouaoud, S. E.; G. Le Borgne *J. Chem. Soc., Dalton Trans.* **1979**, 547.

(16) The crude reaction products were obtained by filtration of the Pd metal formed, evaporation of the solvent, stirring with pentane, filtration, and washing with two 30-mL portions of pentane to remove unchanged alkyne and drying in vacuo. The reaction product was then extracted with ether to give a red solution. The $^1$H NMR spectrum of the evaporated ether extracts showed the presence of 3 as the only identifiable product.

(17) The bulky group on the alkyne usually points away from the Pd center in these reactions. We have frequently found that the an alkoxycarbonyl group may usually be regarded has being bulkier than a phenyl: Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2043. The assignment of the regioisomers **3c,e,n,o,p,q** has been made accordingly. An opposite trend was found for a related study of the reaction of alkynes with cyclometallated manganese compounds: Liebeskind, L. S.; Gasdaska, J. R.; McCallum, J. S. *J. Org. Chem.* **1989**, *54*, 669.

(18) With these alkynes multiple insertion into the Pd–C bond of **2a** may take place as found in related compounds: Rheingold, A. L.; Wu, G.; Heck, R. F. *Inorg. Chim. Acta* **1987**, *131*, 147. Hosokawa, T.; Calvo, C.; Lee, H. B.; Maitlis, P. M. *J. Am. Chem. Soc.* **1973**, *95*, 4914. Dupont, J.; Pfeffer, M.; Daran, J.-C.; Gouteron, J. *J. Chem. Soc., Dalton Trans.* **1988**, 2421.

Scheme II

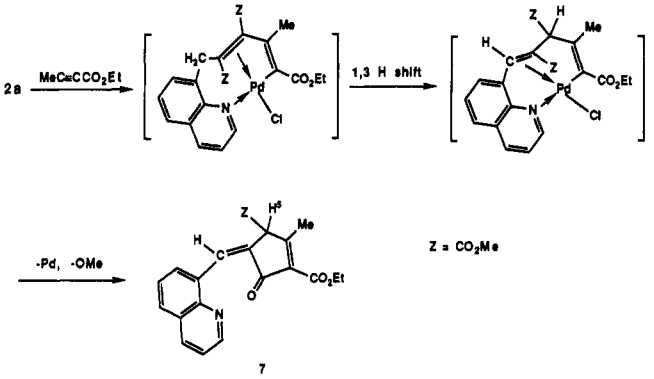
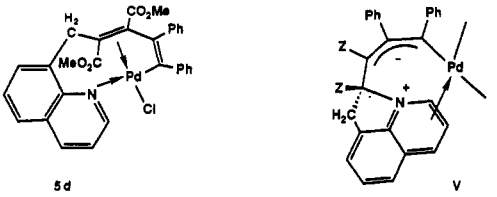


Chart III



5d V

**5a** and **5b**, respectively, were obtained in high yields.

The reaction of **1** and **1*** with ethyl 3-phenylpropynoate (EPP) at elevated temperature led to the formation of the $\alpha$-pyrone **6**. The yield of **6**, which in the case of the chloride bridged dimer is quite moderate, can be drastically improved by using the cationic derivative **5b***.[19] The interpretation of its $^1$H NMR spectrum is straightforward; it shows homotopic $CH_2$ protons even at low temperature and the absence of one ethyl group. The structure of this pyrone derivative, which is shown in Scheme I, was furthermore ascertained by X-ray diffraction studies.[20]

The reaction of **2a** with ethyl but-2-ynoate (Table I, entry 4) gave the corresponding cyclazine **3d** in low yield as a result of the nonregioselective insertion of the unsymmetrical alkyne. Whereas the regioisomer with the methyl substituent on the carbon that is $\sigma$-bound to Pd afforded the cyclazine **3d**, the other regioisomer led to formation of the fulv-3-en-2-one **7** (Scheme II). This compound is most likely formed via the intermediate depicted in Scheme II which is the result of a 1,3 H shift of one of the protons of the quinoline $CH_2$ group.[15a] The formulation of **7** was confirmed by its elemental analysis and mass spectrum. Its $^1$H NMR spectrum shows that the proton $H^5$ of the fulvenone ring is coupled to both the olefinic proton and the methyl unit.

## Discussion

We[17,21a-e] and others[21f,g] have shown on many occasions that insertion of one alkyne into the metal–carbon bond of cyclopalladated amines followed by elimination of the palladium metal can lead to the formation of heterocyclic compounds. This strategy, which is based on a 1:1 Pd/alkyne stoichiometry has been successful for a number of heterocycle syntheses, but not in the case of the 8-mq ligand. As stated earlier, the reaction between **1** and alkynes always has a tendency to form diinsertion products such as **5** even when a strict 1:1 Pd/alkyne stoichiometry is employed (with the noticeable exceptions of the reactions with DMAD and HFB which indeed gave monoinsertion products). In this paper we describe the formation of cyclazines **3** and various other compounds involving several rearrangements of one ester function (compounds **6** and **7**). We have moreover reported in a recent publication about the formation of a cyclobutene adduct of 1*H*-benzo[*ij*]quinolizinium from the reaction of **1** with 2 equiv of DPA per palladium atom.[21a] These new organic systems have in common the fact that they consist of one quinoline unit coupled with two alkynes; however, they are chemically completely different. The course of the reaction is dependent upon the nature of the alkyne substituents.

The mechanism of the reactions leading to **3** can be understood considering that a key step of the reaction is a nucleophilic addition of the quinoline nitrogen on the olefinic unit $\eta^2$-bound to Pd in compounds **5**, analogous to the Michael-type addition of pyridine on an activated alkene.[22] This implies initial decoordination of the N atom, leaving a 14e Pd center. Such electron-deficient intermediates have been proposed to be involved in the well-established reductive elimination process (e.g., elimination of ethane from di(phosphine)dimethylpalladium(II) species) based on theoretical calculations.[23] From this reactive intermediate different pathways can be envisaged most of which are controlled by the substituents on the butadienyl unit.

When the reaction of **2a** with DPA was run at ambient temperature in PhCl, a red brown material was collected. From this material, compounds **5d** and V were isolated under acidic and neutral conditions, respectively, via fractional crystallization. Both products proved to be genuine intermediates for the formation of the parent compound **3b** since when treated with a baselike 4-picoline at room temperature or by thermal degradation in PhCl, no products other than **3b** besides palladium metal could be detected.

Compounds **5d** and V are isomers based on their spectroscopic data. The $^1$H NMR data of the $CH_2$ group and the protons ortho and para to N in **5d** show characteristic chemical shifts and $J_{HH}$ values which indicate that **5d** has a structure analogous to that of **5a**, **5b**, and **5c**, i.e., that of a diinserted nine-membered palladocycle. In marked contrast, the $^1$H NMR spectrum of V indicates that this organopalladium complex has a hitherto unknown geometry as compared to related compounds synthesized with this ligand. Of note is the very high frequency for the ortho, meta, and para protons to N which were found at 4.1, 4.9, and 6.5 ppm, respectively, with $^3J_{HH}$ and $^4J_{HH}$ corresponding to values which are usually found in quinoline systems. This was established by 2D COSY and $^{13}$C–$^1$H correlation spectroscopy. The spectral features of V bear some analogy to those of a related organopalladium compound $[NC_9H_6CH_2C(CF_3)=C(CF_3)]Pd[C(CF_3)=C(CF_3)C_{10}H_6OMe]$ for which the X-ray crystal structure determination shows an aryl ring $\eta^2$-bonded to the Pd center.[24] For this reason, although the characterization

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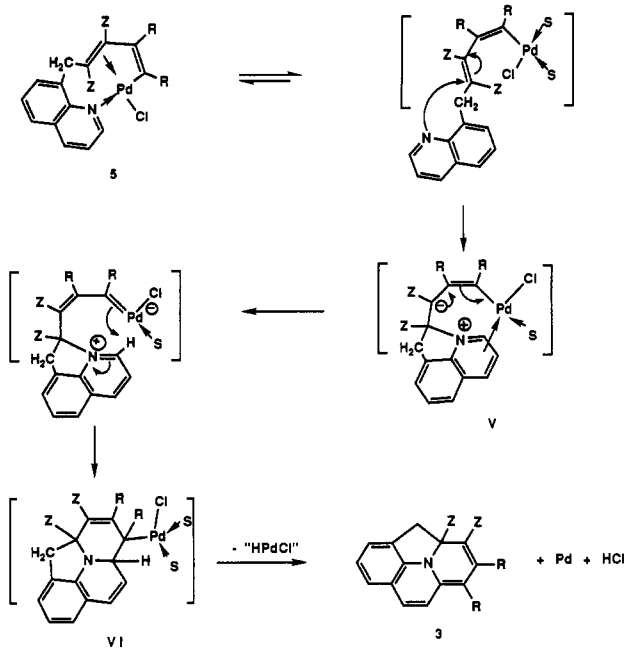
**Scheme III**




of V is far from unambiguous, we propose that in compound V a similar interaction of the quinoline unit to the palladium atom could exist. An aryl $\eta^2$-interaction to Pd as in V has frequently been proposed to precede C–H activation of aryl units by this metal.[25] We have recently suggested that such an interaction exists prior to carboannulation reactions of aryl rings in related organopalladium compounds.[26] A conceivable explanation for the formation of the fused five- and six-membered rings involves, starting from **5d**, a fast, intramolecular, nucleophilic addition of the nitrogen atom on the strongly activated olefinic unit $\eta^2$-bound to Pd. Since both carbons carry an identical electron-withdrawing group ($CF_3$ or $CO_2Me$) the regiochemistry of the C–N bond formation is mainly determined by the nature of the two other substituents, i.e., $CH_2$ vs a vinyl unit. Therefore, the attack takes place at the carbon $\alpha$ positioned to the $CH_2$ group to give the five-membered heterocyclic ring. From this stage the Pd coordination sphere is completed by interaction with the aryl $\pi$-system as a consequence of the high electrophilicity of the Pd center. Insertion of the palladacarbene into the aryl C–H bond should give the final C–C bond in VI from which the product is obtained via a $\beta$-elimination process.

In the case of **5b**, after decoordination of the nitrogen atom as in **5a**, the electron deficiency of the Pd should be easily compensated by coordination of one of the ester oxygen atoms to Pd, resulting in a reactive intermediate. A result of the coordination of the ester function to Pd is that it is now activated in such a way that it may readily lose its ethyl group[27] through nucleophilic attack. This formation of an $\alpha$-pyrone is very similar to the result reported recently by Heck in a related Pd-mediated synthesis of 3,4-diphenylisocoumarin.[28]

As previously stated, the reaction of **2a** with ethylbut-2-ynoate is not regioselective since one regioisomer leads to **3d** (entry 4, Table I) whereas the other affords the new fulvenone **7**. This result illustrates once more the powerful influence of the nature of the substituents on the butadienyl moiety upon the course of the reaction. In the formation of **7** (see Scheme II) the intermediate involved is the only one in this study to have an electron-rich substituent at the carbon $\beta$ with respect to Pd. Therefore, the Michael-type addition of the nitrogen atom cannot take place in the same way as in the related reactions of **2a**, and hence the depalladation leads to another type of compound.

## Conclusion

It has been shown on many occasions that alkyne insertions into the Pd–C bonds of cyclopalladated species can lead, after elimination of the palladium metal, to the formation of heterocyclic compounds via C–N or C–O bond formation. Here we present a novel, facile preparation of tetracyclic ortho- and perifused [2.3.3]cyclazines. The foremost synthetic challenges provided by this cyclazine skeleton are (i) simultaneous formation of a C–C and a C–N bond; (ii) formation of a quaternary center at C-2; and (iii) the regiochemistry at C-3 and C-4. The method described here allows the synthesis of a large class of novel [2.3.3]cyclazines and is superior to previously established procedures which are somewhat limited in scope, provided that the substituents at the positions 4a–7 have been chosen with the appropriate electronegativity.

## Experimental Section

All reagents were commercially obtained and used without further purification. Compounds **1**,[14] **2a**,[15a] **2b**,[15b] phenyl(4-nitrophenyl)ethyne, phenyl(4-methylphenyl)ethyne, phenyl(4-methoxyphenyl)ethyne, phenyl[3-(trifluoromethyl)phenyl]-ethyne,[29] and methylphenyl propiolate[30] were prepared by literature methods. The storage time of **2a** is about 10 d in air; under $N_2$ it can be stored indefinitely. Solvents were appropriately dried and distilled before use. Unless otherwise stated, reactions were run in air. IR spectra were recorded as KBr discs. All other spectroscopic measurements were performed as described previously.[21b,26,31] All NMR spectra were taken in $CDCl_3$. J values are given in Hz.

**Synthesis of the Cyclazines. 4*H*-4a,5,6,7-Tetracarbomethoxyindolo[2,7,1-*cde*]quinolizine (3a).** To a suspension of **1** (2 g, 3.51 mmol) in chlorobenzene (100 mL) was added DMAD (2.1 g, 14.8 mmol). The mixture was stirred at 100 °C for 30 min after which the solvent was evaporated in vacuo. The residue was extracted with 2 × 50 mL of $CH_2Cl_2$, and the extract was filtered through Celite to eliminate metallic palladium. The orange filtrate was concentrated to ca. 20 mL and chromatographed on an alumina column (10 cm, Merck Aluminiumoxid 90, standard grade, activity II/III, 70–230 mesh). Elution with $CH_2Cl_2$ removed the excess alkyne and impurities. The product eluted with acetone gave an orange solution which after evaporation of the solvent in vacuo afforded 1.36 g (91%) of **3a**. Crystals were obtained from a $CH_2Cl_2$/hexane mixture: orange prisms, mp 225–226 °C; $^1H$ NMR $\delta$ 8.40 and 7.78 (2d, 2 H, $H^9$ and $H^8$, $^3J_{HH}$ = 9.6), 7.53–7.3 (m, 3 H, $H^{ar}$), 4.14 and 3.91 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 17.5), 3.88, 3.79, 3.77 and 3.62 (4s, 12 H, $4CH_3$); the numbering of the atoms of the cyclazines refers to that used in Table I; $^{13}C$ NMR $\delta$ 170.5, 168.7, 165.2 and 163.9 (4 CO), 145.8, 143.9, 139.8, 134.2, 129.2, 126.2, 125.5, 123.6, 122.2, 121.4, 71.0 ($C^{4a}N$), 53.4, 52.4, 51.8, 51.2 ($4CH_3O$), 41.3 ($CH_2$); IR ($cm^{-1}$) 1740 (vs), 1729 (vs), 1699 (vs), 1676

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(vs); UV/vis [λ (nm), ε] 470 (4547), 353 (4719), 300 (10 918), 245 (14 594); m/z 425 ($M^+$), 395, 366 ($M^+ - CO_2Me$) and 344. Anal. Calcd for $C_{22}H_{19}NO_8$: C, 61.95; H, 4.59; N, 3.29. Found: C, 61.6; H, 4.4; N, 3.15.

**4*H*-4a,5-Dicarbomethoxy-6,7-diphenylindolo[2,7,1-*cde*]quinolizine (3b).** To a stirred suspension of **2a** (0.534 g, 0.63 mmol) in 1,2-dichloroethane (80 mL) was added DPA (0.266 g, 1.29 mmol). The resulting mixture was refluxed for 15 h after which the metallic palladium was removed by filtration through Celite. The deep purple filtrate was evaporated to dryness in vacuo and washed with two 50-mL portions of cold hexane. The nearly black residue was chromatographed on an alumina column (6 cm). Elution with pentane/$CH_2Cl_2$ (1:1) eliminated unreacted DPA and undesirable side products. This was followed by elution with $CH_2Cl_2$/acetone (1:1) to give a dark purple solution which was evaporated to dryness: yield 0.300 g (52%) of purple **3b**; $^1H$ NMR δ 7.3–6.78 (m, 14 H, $H^{ar}$), 6.75 (d, 1 H, $H^8$), 4.10 and 3.90 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 17.4), 3.7 and 3.33 (2s, 6 H, $2CH_3$); $^{13}C$ NMR δ 172.9, 166.3 (2 CO), 141.7, 140.6, 138.4, 136.6, 132.3, 131.9, 130.3, 129.7, 129.2, 128.9, 128.1, 127.9, 127.7, 127.2, 126.9, 129.7, 126.2, 126.0, 124.9, 123.7, 123.0, 121.1, 120.7, 70.1 ($C^{4a}N$), 52.7, 50.5 (2 $CH_3O$), 41.8 ($CH_2$); IR ($cm^{-1}$) 1731 (vs), 1671 (vs); UV/vis [λ (nm), ε] 531 (3958), 382 (3193), 294 (10 792), 243 (20 792), 236 (20 290); m/z 461 ($M^+$), 402 ($M^+ - CO_2Me$). Anal. Calcd for $C_{30}H_{23}NO_4$: C, 78.07; H, 5.02; N, 3.03. Found: C, 76.9; H, 5.1; N, 3.0.

**4*H*-4a,5-Dicarbomethoxy-6-carbethoxy-7-phenylindolo[2,7,1-*cde*]quinolizine (3c).** To a stirred suspension of **2a** (1.23 g, 1.44 mmol) in 1,2-dichloroethane (100 mL) was added EPP (0.49 mL, 2.96 mmol). The resulting mixture was refluxed for 18 h, after which the metallic palladium was removed by filtration through Celite. The red-purple filtrate was evaporated to dryness in vacuo and washed with two 50-mL portions of cold hexane. After purification on an alumina column (as in the preparation of **3b**) the yield was 700 mg (55%) of purple **3c**. Crystals suitable for X-ray diffraction studies were obtained from a 4-picoline/$Et_2O$/pentane mixture: $^1H$ NMR δ 7.38–7.1 (m, 9 H, $H^{ar}$), 6.70 (d, 1 H, $H^8$), 4.10 (s, 2 H, $CH_2$), 3.95 (dq($ABX_3$), 2 H, $CH_2CH_3$), 3.78 and 3.69 (2s, 6 H, $2CH_3$), 0.97 (t, 3 H, $CH_2CH_3$, $^3J_{HH}$ = 7.17); $^{13}C$ NMR δ 172.0, 167.9, 164.8 (3 CO), 150.3, 144.8, 141.0, 140.4, 134.7, 132.0, 131.2, 128.7, 128.2, 127.6, 127.4, 125.1, 124.4, 123.3, 120.9, 120.6, 106.1, 97.3, 70.5 ($C^{4a}N$), 60.9 ($CH_2CH_3$), 52.9, 51.3 (2 $CH_3O$), 41.9 ($CH_2$), 13.7 ($CH_2CH_3$); IR ($cm^{-1}$) 1732 (vs, br), 1686; UV/vis [λ (nm), ε] 531 (7625), 387 (4875), 294 (10 250), 243 (27 000); m/z 457 ($M^+$), 398 ($M^+ - CO_2Me$). Anal. Calcd for $C_{27}H_{23}NO_6$:C, 70.89; H, 5.06; N, 3.06. Found: C, 70.8; H, 5.0; N, 3.0.

**4*H*-4a,5-Dicarbomethoxy-6-carbethoxy-7-methylindolo[2,7,1-*cde*]quinolizine (3d).** To a stirred suspension of **2a** (1.244 g, 1.46 mmol) in 1,2-dichloroethane (150 mL) was added EMP (0.30 g, 3.12 mmol) and 0.250 g of polyvinylpyridine. The resulting mixture was kept at reflux temperature for 16 h, after which the metallic palladium and other solid materials were removed by filtration through Celite. The red-purple filtrate was evaporated to dryness in vacuo and the residue washed with two 50-mL portions of hexane cooled to 0 °C. The product was extracted with 3 × 100 mL of ether ($Et_2O$). The combined ether extracts were concentrated to ca. 10 mL, and 10 mL of pentane was added. The mixture was chromatographed on an alumina column prepared from a pentane slurry. Elution with $Et_2O$/pentane (1:3) (ca. 120 mL) followed by pure $Et_2O$ gave an orange fraction which contained **7**. Elution with $CH_2Cl_2$ gave a purple fraction which contained **3d**. After evaporation of the solvent the yield of **3d** was 98 mg (9%): $^1H$ NMR δ 7.32–7.27 (m, 2 H, $H_{1,3}$), 7.11 (t, 1 H, $CH_2$), 7.38 and 6.97 (2d (AB), 2 H, $H^9$ and $H^8$, $^3J_{HH}$ = 9.4), 4.38 (q, 2 H, $CH_2$, $^3J_{HH}$ = 7.2), 4.05 and 3.95 (2d(AB), 2 H, $CH_2$, $^2J_{HH}$ = 17), 3.77 and 3.62 (2s, 6 H, 2 $OCH_3$), 1.91 (s, 3 H, $CH_3$); 1.38 (t, 3 H, $CH_2CH_3$); $^{13}C$ NMR δ 173.3, 169.4, 165.1 (3 CO), 149.4, 137.0, 131.8, 128.2, 126.3, 125.8, 124.6, 122.8, 122.0, 120.8, 119.9, 97.2, 69.4, 61.4, 46.4, 41.7, 32.9, 13.8, 11.0, IR ($cm^{-1}$) 1731 (s, br), 1679 (s, br); UV/vis [λ (nm), ε] 542 (6050), 399 (4150), 311 (6275), 241 (21 000); m/z 395 ($M^+$), 336 ($M^+ - CO_2Me$). Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.6; H, 5.5; N, 3.3.

**4*H*-4a,5,6-Tris(methoxycarbonyl)-7-phenylindolo[2,7,1-*cde*]quinolizine (3e).** To a stirred suspension of **2a** (0.750 g, 0.88 mmol) in 1,2-dichloroethane (80 mL) was added MPP (0.300 g, 1.87 mmol), and the resulting mixture was refluxed for 14 h. The solvent was then evaporated in vacuo and the residue washed with two 50-mL portions of pentane. The product was extracted with $CHCl_3$ and chromatographed on an alumina column (10 cm). Elution with $CHCl_3$ was continued until the eluate became colorless. Evaporation to dryness of the deep red $CHCl_3$ fractions yielded 0.500 g (64%) of **3e**: $^1H$ NMR δ 7.37–7.17 (m, 9 H, $H^{ar}$), 6.68 (d, 1 H, $H^8$), 4.09 (s, 2 H, $CH_2$), 3.79, 3.68, and 3.50 (3s, 9 H, $3CH_3$); $^{13}C$ NMR δ 171.7, 168.3, 164.7 (3 CO), 144.5, 140.8, 140.4, 134.5, 131.6, 131.1, 130.1, 129.1, 128.6, 128.1, 127.9, 127.7, 127.4, 127.2, 124.0, 124.3, 123.1, 120.7, 120.4, 105.9, 70.4 ($C^{4a}N$), 52.7, 51.6, 51.2 (3 $CH_3O$), 41.7 ($CH_2$); IR ($cm^{-1}$) 1735 (vs, br), 1677; UV/vis [λ (nm), ε] 531 (10 398), 389 (6615), 293 (13 849), 241 (38 363); m/z 443 ($M^+$), 384 ($M^+ - CO_2Me$). Anal. Calcd for $C_{26}H_{20}NO_6$: C, 70.58; H, 4.56; N, 3.17. Found: C, 70.6; H, 4.4; N, 3.1.

**4*H*-4a,5-Bis(methoxycarbonyl)-7(or 6)-phenyl-6(or 7)-(*p*-nitrophenyl)indolo[2,7,1-*cde*]quinolizine (3f).** To a stirred suspension of **2a** (0.498 g, 0.58 mmol) in 1,2-dichloroethane (100 mL) was added phenyl(4-nitrophenyl)acetylene (0.265 g, 1.2 mmol). A deep red solution was obtained after 0.5 h at reflux, which was continued for an additional 9 h. The solvent was then evaporated in vacuo to produce a black residue, which was washed with 100 mL of hexane. The product was extracted with $CH_2Cl_2$, and the metallic palladium was removed by filtration through Celite. The extract was concentrated to ca. 20 mL, and 20 mL of pentane was added. This mixture was chromatographed on a alumina column prepared with pentane. Elution with $CH_2Cl_2$ gave first a small yellow fraction which contained impurities and side products. The second, deep red fraction contained **3f** and **3g**. After removal of the solvent in vacuo the yield was 0.238 g (42%) of a 1:1 mixture of **3f** and **3g**: $^1H$ NMR δ 8.02–7.88 (m, 2 H, *p*-$ArNO_2$), 7.40–6.72 (m, 12 H, $H^{ar}$), 4.15 and 3.94 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 17.2), 3.74, 3.73, 3.41 and 3.37 (4s, 6 H, $2CH_3$); $^{13}C$ NMR δ 172.4, 166.0 (2 CO), 145.7, 144.6, 141.4, 139.9, 138.5, 132.7, 132.3, 131.5, 130.1, 129.5, 129.1, 128.9, 128.2, 128.1, 127.4, 126.9, 126.6, 125.3, 124.3, 123.3, 122.9, 120.8, 119.9, 71.0 ($C^{4a}N$), 52.8, 50.6, 41.6, 42.1, 29.3; IR ($cm^{-1}$) 1730 (vs) and 1671 (vs); UV/vis [λ(nm), ε] 522 (5009), 383 (4296), 245 (18 462); m/z 506 ($M^+$), 447 ($M^+ - CO_2Me$). Anal. Calcd for $C_{30}H_{22}N_2O_6$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.0; H, 4.5; N, 5.4.

**4*H*-4a,5-Bis(methoxycarbonyl)-6(or 7)-phenyl-7(or 6)-[*m*-(trifluoromethyl)phenyl]indolo[2,7,1-*cde*]quinolizine (3h).** To a stirred suspension of **2a** (0.511 g, 0.60 mmol) in 1,2-dichloroethane (90 mL) was added phenyl[3-(trifluoromethyl)phenyl]acetylene (0.310 g, 1.26 mmol). After 0.6 h at reflux temperature an orange solution was formed which became deep red after an additional 0.3 h of heating. Refluxing was continued for 11 h, after which the solvent was evaporated in vacuo. The product was extracted from the black residue with 50 mL of $CH_2Cl_2$ and filtered through Celite to remove the Pd metal. The deep purple product was chromatographed on a alumina column (6 cm). Elution with $CH_2Cl_2$ gave first a deep purple fraction which contained **3h**. The second orange fraction contained traces of **3a** (traces of **3a** are sometimes present in the starting material **2a**) and side products. After removal of the solvent in vacuo the yield was 0.350 g (55%) of a 1:2 mixture of **3h** and **3i**: $^1H$ NMR δ 7.39–6.68 (m, 14 H, $H^{ar}$), 4.14 and 3.96 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 17.1), 3.74, 3.73, 3.37 and 3.36 (4s, 6 H, $2CH_3$); $^{13}C$ NMR δ 172.7, 166.2, 165.8 (2 CO), 150.8, 149.8, 141.5, 140.1, 138.5, 137.6, 135.9, 135.5, 134.6, 132.4, 132.0, 131.7, 131.0, 130.7, 129.0, 128.7, 128.4, 128.1, 127.9, 127.2, 126.9, 126.3, 125.1, 125.0, 124.0, 123.2, 122.7, 120.9, 120.4, 108.4, 101.1, 70.9 ($C^{4a}N$), 52.8, 50.6, 41.9; IR ($cm^{-1}$) 1731 (s, sh), 1675 (s, br); UV/vis [λ (nm), ε] 529 (7235), 392 (4946), 298 (14 319), 281 (14 989), 242 (32 030); m/z 529 ($M^+$), 470 ($M^+ - CO_2Me$). Anal. Calcd for $C_{31}H_{22}F_3N_1O_4$: C, 70.32; H, 4.19; N, 2.64. Found: C, 69.1; H, 4.2; N, 2.2.

**4*H*-4a,5-Bis(trifluoromethyl)-6,7-dicarbomethoxyindolo[2,7,1-*cde*]quinolizine (3l).** To a stirred suspension of **2b** (0.512 g, 0.57 mmol) in PhCl (40 mL) at 80 °C was added dropwise DMAD (0.15 mL, 1.22 mmol) over 0.4 h, and the resulting mixture was heated at 100 °C for 6 h. The solvent was evaporated in vacuo and the black residue extracted with two 100-mL portions of $CH_2Cl_2$. The palladium-black was filtered off through Celite, and the filtrate was chromatographed on a silica gel column (8 cm). Elution with $CH_2Cl_2$ gave a bright yellow solution which was concentrated to ca. 10 mL. Hexane (100 mL) was added and **3l**

separated out. The supernatant liquids were reconcentrated to ca. 10 mL on a rotatory evaporator (without heating), and 298 mg (58%, total yield) of **3l** was collected by filtration: $^1$H NMR $\delta$ 8.31 and 7.71 (2d, 2 H, H$^9$ and H$^8$, $^3J_{HH}$ - 9.67), 7.68–7.34 (m, 3 H, H$^{ar}$), 3.96 (s, 2 H, $CH_2$), 3.89 and 3.79 (2s, 6 H, $2CH_3$); $^{13}$C NMR $\delta$ 165.1, 164.8 (2 CO), 145.5, 139.6, 134.0, 133.7, 128.2, 127.1, 126.5, 126.2, 125.4, 125.0, 124.8, 123.8, 122.4, 121.5, 53.4, 52.7, 51.4, 37.3; IR (cm$^{-1}$) 1744 (vs, br), 1697 (m); $\nu$ CF 1253 (s), 1232 (s), 1217 (s), 1175 (s); UV/vis [$\lambda$ (nm), $\epsilon$] 452 (10 382), 289 (12 964), 237 (27 454); $m/z$ 445 (M$^+$), 376 (M$^+$ - $CF_3$) and 259. Anal. Calcd for $C_{20}H_{13}F_6NO_4$: C, 53.94; H, 2.94; N, 3.14. Found: C, 53.7; H, 3.0; N, 3.0.

**4*H*-4a,5-Bis(trifluoromethyl)-6,7-diphenylindolo[2,7,1-*cde*]quinolizine (3m).** To a stirred suspension of **2b** (0.534 g, 0.6 mmol) in PhCl (35 mL) at 80 °C was added dropwise a solution of DPA (0.230 g, 1.29 mmol) in PhCl (10 mL). The resulting mixture was kept at 100 °C for 7 h, after which the solvent was removed in vacuo. The residue was washed with two 50-mL portions of pentane cooled to 0 °C and the product extracted with 200 mL of a ca. 5% solution of diethylamine in $Et_2O$. The extract was evaporated to dryness in vacuo. An orange-red solution was obtained upon extraction with $Et_2O$ and the extract filtered through Celite. The filtrate was evaporated to dryness and dried in vacuo. Yield 0.298 g (50%). Analytically pure **3m** should be obtained by fractional crystallization, e.g., by slow evaporation of the $Et_2O$ solution since **3m** decomposes on either alumina or silica gel. Yield after crystallization is 0.041 g (7%): red cubes, mp 111–113 °C ($Et_2O$); $^1$H NMR $\delta$ 7.58–6.94 (m, 14 H, H$^{ar}$), 6.44 (d, 1 H, H$^8$), 3.94 (s, 2 H, $CH_2$); $^{13}$C NMR $\delta$ 141.3, 137.1, 135.6, 132.2, 131.9, 131.6, 129.7, 129.0, 128.4, 127.8, 126.9, 126.4, 125.3, 124.1, 123.8, 123.3, 121.9, 120.8, 110.2, 76.4, 39.3 ($CH_2$); IR (cm$^{-1}$) 1200, 1187, 1163; UV/vis [$\lambda$ (nm), $\epsilon$] 299 (10 422), 223 (19 400). Anal. Calcd for $C_{28}H_{17}F_6N$: C, 69.86; H, 3.56; N, 2.91. Found: C, 70.6; H, 4.3; N, 3.2. These elemental analyses were carried out several times in presence of a catalyst ($V_2O_5$) to produce the best results.

**4*H*-4a,5-Bis(trifluoromethyl)-6-carbethoxy-7-phenylindolo[2,7,1-*cde*]quinolizine (3n).** To a stirred suspension of **2b** (0.692 g, 0.78 mmol) in PhCl (55 mL) at 80 °C was added dropwise EPP (0.27 mL, 1.63 mmol), and the resulting mixture was stirred at 110 °C for 2 h. After removal of the solvent in vacuo, the residue was washed with 15 mL of pentane cooled to 0 °C, and the product was extracted with two 100-mL portions of $Et_2O$. The ether fractions were dried in vacuo to yield 0.576 g (78 %) of crude **3n** + **3o**. The product **3n** was isolated by slow evaporation of a saturated solution of petroleum ether (65–95 °C) followed by crystallization at -20 °C to give microcrystals: $^1$H NMR (major isomer, **3n**) $\delta$ 7.4–7.14 (m, 8 H, H$^{ar}$), 7.11 and 6.55 (2d, 2 H, H$^9$ and H$^8$, $^3J_{HH}$ = 9.6), 3.91 (s, 2 H, $CH_2$), 3.94 (q, 2 H, $CH_2CH_3$), 0.97 (t, 3 H, $CH_2CH_3$, $^3J_{HH}$ = 7.16); (minor isomer, **3o**) $\delta$ 6.80 (d, 1 H, H$^9$), 4.20 (m, ABX$_3$ pattern, 2 H, $CH_2CH_3$), 4.08 (s, 2 H, $CH_2$), 1.27 (t, 3 H, $CH_2CH_3$). The following data are those of **3n**: $^{13}$C NMR $\delta$ 166.2; 141.0, 138.4, 134.2, 131.9, 131.7, 130.9, 129.7, 128.4, 128.3, 128.0, 127.7, 125.9, 125.2, 124.7, 124.5, 124.4, 123.5, 123.2, 121.0, 120.9, 105.4, 61.5, 37.9, 13.8; IR (cm$^{-1}$) 1735 (s, br); UV/vis [$\lambda$ (nm), $\epsilon$] 491 (3622), 234 (17 928); $m/z$ 477 (M$^+$), 409, 408 (M$^+$ - $CF_3$). Anal. Calcd for **3n**, $C_{25}H_{17}F_6NO_2$: C, 62.90; H, 3.59; N, 2.93. Found: C, 63.8; H, 4.0; N, 3.0. These elemental analyses were carried out several times in the presence of a catalyst ($V_2O_5$), to produce the best results.

**4*H*-4a,5-Bis(trifluoromethyl)-6-carbomethoxy-7-phenylindolo[2,7,1-*cde*]quinolizine (3p).** To a stirred suspension of **2b** (1.60 g, 1.79 mmol) in PhCl (100 mL) was added dropwise MPE (0.61 g, 3.8 mmol), and the resulting mixture was kept at 110 °C for 2 h. After removal of the solvent the residue was washed with pentane cooled to 0 °C. The orange washings were discarded, and **3p** and **3q** were extracted with $Et_2O$. Yield 1.091 g (67%) of crude **3p** + **3q**. Yield of pure **3p** after fractional crystallization from a saturated $Et_2O$ solution was 180 mg (11%): red cubes, mp 164–166 °C ($Et_2O$); $^1$H NMR (major isomer, **3p**) $\delta$ 7.12 and 6.56 (2d, 2 H, H$^9$ and H$^8$, $^3J_{HH}$ = 9.6), 3.91 (s, 2 H, $CH_2$), 3.47 (s, 3 H, $CH_3$); (minor isomer, **3q**) $\delta$ 6.65 (d, H$^9$), 4.09 (s, 2 H, $CH_2$), 3.78 (s, 3 H, $CH_3$). The following data are those of **3p**: $^{13}$C NMR $\delta$ 166.7 (CO), 140.9, 138.5, 134.2, 131.7, 131.4, 131.2, 129.8, 128.5, 128.4, 128.3, 127.7, 127.4, 127.3, 125.2, 124.8, 124.6, 124.4, 124.1, 123.5, 123.3, 121.1, 120.9, 105.3, 52.1, 51.8, 37.8 ($CH_2$); IR (cm$^{-1}$) 1739 (s, br); $\nu$ CF 1196 (s), 1185 (s), 1169 (s, br), 1155 (s); UV/vis [$\lambda$ (nm), $\epsilon$] 493 (7782), 370 (4673), 285 (8054), 234 (27 236); $m/z$ 463 (M$^+$), 394 (M$^+$ - $CF_3$). Anal. Calcd for **3p**, $C_{24}H_{15}F_6NO_2$: C, 62.21; H, 3.26; N, 3.02. Found: C, 63.1; H, 3.4; N, 3.1.

**[Pd(Ph)C=C(CO$_2$Et)C(Ph)=C(CO$_2$Et)CH$_2$C$_9$H$_6$N Cl] (5b).** To a suspension of **1** (0.628 g, 1.11 mmol) in PhCl (50 mL) was added EPP (0.73 mL, 4.42 mmol), and the resulting mixture was stirred for 5 d at room temperature. Unreacted **1** was filtered off and the orange filtrate evaporated to dryness in vacuo. The residue was washed with pentane (3 × 50 mL) to eliminate traces of alkyne and dryed in vacuo to give 1.005 g (72%) of beige-yellow **5b** as the sole regioisomer: $^1$H NMR $\delta$ 9.82 (dd, 1 H, H$^o$, $^4J_{HH}$ = 1.7, $^3J_{HH}$ = 5.1), 8.17 (dd, 1 H, H$^p$, $^3J_{HH}$ = 8.2), 8.03–7.24 (m, 14 H, H$^{ar}$), 4.18 (dq (ABX$_3$), 2 H, $CH_2CH_3$), 3.88 (q, 2 H, $CH_2CH_3$), 3.97 and 3.76 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 15), 1.06 and 0.91 (2t, 6 H, $2CH_3$, $^3J_{HH}$ = 7.1); the numbering of the hydrogens as o, m, and p refers to the hydrogens ortho, meta, and para to the N atom of the quinoline ring; $^{13}$C NMR $\delta$ 167.7, 159.5 (2 CO), 156.7, 156.4, 144.7, 139.2, 138.3, 135.7, 135.6, 132.6, 130.9, 130.3, 128.9, 128.7, 128.0, 127.7, 127.0, 126.3, 120.7, 103.7, 95.1, 61.8, 59.8, 36.7, 13.8, 13.6. IR (cm$^{-1}$) 1711 (vs, br). Anal. Calcd for $C_{32}H_{28}ClNO_4Pd$: C, 60.77; H, 4.46; N, 2.22. Found: C, 61.5; H, 4.5; N, 2.1.

**[Pd(Ph)C=C(CO$_2$Me)C(Ph)=C(CO$_2$Me)CH$_2$C$_9$H$_6$N Cl] (5c).** To a stirred suspension of **1** (0.507 g, 0.89 mmol) in PhCl (30 mL) was added dropwise MPP (0.57 g, 3.56 mmol). The resulting mixture was heated 0.5 h at ca. 80 °C, after which an orange-brown solution was obtained. After filtration through Celite to remove traces of palladium metal, the solvent was removed in vacuo and the residue was stirred with pentane (100 mL) to remove unchanged alkyne and impurities. The light-brown solid thus obtained was filtered off and dried in vacuo to give 0.900 g (84%) of **5c** as a mixture of two regioisomers. The product was purified by chromatography on a small silica gel column using $CH_2Cl_2$ as eluant and crystallized by adding hexane to a $CH_2Cl_2$ solution: yellow needles; $^1$H NMR $\delta$ 9.81 (dd, 1 H, H$^o$), 8.17 (dd, 1 H, H$^p$), 8.01 (m, 1 H, H$^{ar}$), 7.70–7.27 (m, 13 H, H$^{ar}$), 3.99 and 3.77 (2d, 2 H, $CH_2$, $^2J_{HH}$ = 14), 3.73 and 3.45 (2s, 6 H, 2 $OCH_3$). Anal. Calcd for $C_{30.5}H_{25}Cl_2NO_4Pd$ (**5c** + 0.5 $CH_2Cl_2$): C, 56.60; H, 3.88; N, 2.17. Found: C, 55.7; H, 3.7; N, 2.3. (Despite repeated crystallizations, no better analyses could be obtained.)

**Synthesis of the Intermediates 5d and V.** To a stirred suspension of **2a** (0.534 g, 0.63 mmol) in PhCl (80 mL) was added DPA (0.266 g, 1.29 mmol). The mixture was stirred at room temperature during 3 d affording a red solution from which unchanged **2a** was removed by filtration. The solvent was removed in vacuo, and the red residue was divided into two parts. The first was dissolved in $CHCl_3$ (5 mL) to which glacial acetic acid (1 mL) and pentane (ca. 15 mL) were added affording orange-yellow crystals of **5d**. The second portion was dissolved in $CH_2Cl_2$ (5 mL) to which slow addition of hexane caused the crystallization of V as dark-red crystals: $^1$H NMR of **5d** $\delta$ 10.20 (d, $^1$H, H$^o$), 8.22 (d, 1 H, H$^p$), 7.82–6.79 (m, 14 H, H$^{ar}$), 4.12 and 2.62 (2 s, 6 H, 2 $OCH_3$), 3.97 and 2.43 (2dd, 2 H, $CH_2$, $^2J_{HH}$ = 17.6); $^1$H NMR of V $\delta$ (major isomer) 7.72–6.55 (m, 12 H, Ar), 6.475 (dd, 1 H, H$^p$, $^4J_{H^oH^p}$ = 1.3), 6.28 (m, 1 H, H$^{ar}$), 4.955 (dd, 1 H, H$^m$, $^3J_{H^pH^m}$ = 9.65, $^3J_{H^oH^m}$ = 5.5), 4.12 (dd, 1 H, H$^o$), 4.06 and 3.30 (2d (AB spin system), 2 H, $CH_2$, $^2J_{HH}$ = 16.7), 3.95 and 3.02 (2s, 6 H, 2 $CO_2CH_3$); a second isomer whose importance is ca. 1/4 of the latter can be detected [$\delta$ 5.07 (dd, 1 H, H$^m$), 4.29 (dd, 1 H, H$^o$), 3.98 and 3.11 (2d, 2 H, $CH_2$), 3.93 and 3.19 (2s, 6 H, $2CO_2CH_3$) (the assignment of the signals to the different protons was made by 2D COSY and $^{13}$C–$^1$H correlation spectra); $^{13}$C NMR $\delta$ 133–122 (11s, C Ar), 121.3 (C$^m$), 59.1 (C$^o$), 5.32 and 51.2 ($OCH_3$), 37.9 ($CH_2$). Anal. Calcd for $C_{30}H_{24}ClNO_4Pd$: C, 59.62; H, 4.00; N, 2.32. Found: C, 59.7; H, 4.1; N, 2.3. (Satisfactory analyses could only be obtained for V).

**Synthesis of the 1,2-Pyrone 6.** To a solution of **5b** (0.348 g, 0.56 mmol) in 10 mL of a mixture of $CH_2Cl_2$/MeCN (9:1) was added solid $AgBF_4$ (0.12 g). The AgCl which separated out instantly was removed by filtration through Celite after 10 min of stirring at rt. The pale yellow filtrate was evaporated to dryness in vacuo. The obtained cation **5b*** was dissolved in PhCl (30 mL) and refluxed at a pressure of ca. 10 mm. The pressure was reduced approximately every 10 min. The color changed from pale yellow via dark green to black concomitant with formation of palladium metal. After 0.75 h the black solution was evaporated to dryness

and the residue stirred with 100 mL of pentane to give a green-yellow powder. The product was extracted from the powder with three 50-mL portions of $CH_2Cl_2$ and the extract filtered through Celite to remove metallic palladium. The green-yellow filtrate was flash chromatographed on an alumina column prepared with pentane. The first, orange, fraction eluted with $CH_2Cl_2$ contained the product. After removal of the solvent and drying in vacuo the yield of **6** was 0.250 g (96%). Crystals were grown from a $CH_2Cl_2$/hexane mixture, yellow prisms, mp 151 °C: $^1H$ NMR $\delta$ 8.79 (dd, 1 H, $H^o$, $^4J_{HH}$ = 1.8, $^3J_{HH}$ = 4.2), 8.08 (dd, 1 H, $H^p$, $^3J_{HH}$ = 8.3), 7.34 (dd, 1 H, $H^m$), 7.74-7.17 (m, 13 H, $H^{ar}$), 4.44 (s, 2 H, $CH_2$), 3.88 (q, 2 H, $CH_2CH_3$), 0.79 (t, 3 H, $CH_3$, $^3J_{HH}$ = 7.1); $^{13}C$ NMR $\delta$ 165.9, 161.8, 157.46, 152.6, 148.9, 156.2, 137.6, 136.3, 135.2, 130.8, 128.5, 128.2, 128.1, 127.9, 127.6, 127.4, 126.3, 123.9, 120.8, 61.6, 29.3, 13.3; IR ($cm^{-1}$) 1735 (vs) and 1715 (vs). Anal. Calcd for $C_{30}H_{23}NO_4$: C, 78.09; H, 4.99; N, 3.04. Found: C, 78.2; H, 4.9; N, 3.0.

**Synthesis of the Fulvenone 7.** The crude product was obtained as described for compound **3d**. Crystals were grown by layering hexane on a $CH_2Cl_2$ solution. The yellow crystals which formed rapidly were separated from the solution and washed with cold hexane: yield 0.065 g (12%); $^1H$ NMR $\delta$ 8.98 (dd, 1 H, $H^o$), 8.80 (d, 1 H, $H^{olef}$, $^4J_{HH}$ = 1.4), 8.21-7.44 (m, 5 H, Ar), 4.94 (q, 1 H, $H^5$), 4.32 (dq ($ABX_3$), 2 H, $CH_2$), 3.26 (s, 3 H, $OCH_3$), 2.30 (d, 3 H, $CH_3$, $^4J_{HH}$ = 2.0), 1.34 (t, 3 H, $CH_2CH_3$, $^2J_{HH}$ = 7.1); IR ($cm^{-1}$) 1747 (vs), 1716 (vs), and 1695 (vs); $m/z$ 365 ($M^+$), 306 (M - $CO_2Me$), 292 (M - $CO_2Et$). Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.5; H, 5.3; N, 3.9.

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**Registry No.** 1, 28377-73-3; **2a**, 126205-17-2; **2b**, 71340-03-9; **3a**, 126309-70-4; **3b**, 139243-66-6; **3c**, 126309-72-6; **3d**, 139243-67-7; **3e**, 139243-68-8; **3f,3g**, 126309-73-7; **3g,3f**, 139243-69-9; **3h,3i**, 139243-70-2; **3i,3h**, 126346-80-3; **3l**, 126309-74-8; **3m**, 126309-75-9; **3n**, 139243-71-3; **3o**, 139243-72-4; **3p**, 139243-73-5; **3q**, 139243-74-6; **5b**, 126606-12-0; **5b***, 139243-77-9; **5c**, 139275-99-3; **5d**, 126205-18-3; **6**, 136745-53-4; **7**, 139243-75-7; V, 126460-88-6; DMAD, 762-42-5; HFB, 692-50-2; PhC≡CPh, 501-65-5; PhC≡$CCO_2Et$, 2216-94-6; MeC≡$CCO_2Et$, 4341-76-8; PhC≡$CCO_2Me$, 4891-38-7; PhC≡C-*p*-$C_6H_4NO_2$, 1942-30-9; PhC≡C-*m*-$C_6H_4CF_3$, 126309-76-0; PhC≡C-*p*-$C_6H_4CH_3$, 3287-02-3; PhC≡C-*p*-$C_6H_4OCH_3$, 7380-78-1.

**Supplementary Material Available:** Figures 1 and 2 showing the X-ray crystal structures of the compounds **3a** and **3c**, respectively, X-ray data, and tables of bond lengths, bond angles, positional parameters, and general temperature factors for **3a** and **3c** (19 pages). Ordering information is given on any current masthead page. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# *Notes*

## Chemoenzymatic Approach to Carbohydrate-Derived Analogoues of Platelet-Activating Factor

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Platelet-activating factor (PAF) (Figure 1), a class of phospholipids with a 1-*O*-alkyl-2-*O*-acetylglycero-3-phosphocholine structure, are highly potent mediators of many biological and physiological activities, among which the ability to aggregate platelets and to lower blood pressure.[1]

In two articles, P. Braquet and J. J. Godfroid[2] reported a study on PAF binding sites and on PAF isosteres which led, after QSAR analysis, to interesting conclusions about the nature and the conformation of the binding site. According to the above authors, many potent antagonists of PAF incorporate a tetrahydrofuran ring in which the oxygen atom is ideally placed for interaction with the binding site; moreover, the antagonistic behavior is often associated to the rigidity imposed by the cycle to the backbone. Finally, the lipidic and the polar arms are placed at the opposite end of the molecules.

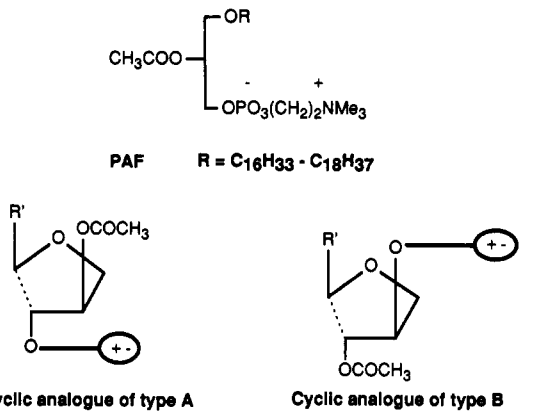


**Figure 1.**

Following the above conclusions, we planned to synthesize and test carbohydrate-derived analogues of PAF of type A and B in which the above requisites are obeyed.

In this paper we describe the stereospecific synthesis of the cyclic analogues of PAF, **10-17**.

Our synthetic scheme starts from the commercially available 2,3,5-tetra-*O*-benzyl-D-arabinose (**1**), which possesses the appropriate skeleton for the synthesis of derivatives of type A and B, provided that (1) the anomeric center is reduced, (2) the hydroxyl group at C-5 is substituted with a long-chain alkyl group, and (3) the hydroxyl groups at C-2 and/or at C-3 are selectively acetylated and consequently the other hydroxyl group is properly func-

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