(q), 28.0 (t), 31.4 (t), 38.3 (s), 41.6 (t), 48.6 (t), 63.6 (d), 177.3 (s), and phenyl signals; high-resolution mass spectrum, $M^+$ calcd for $C_{15}H_{20}NOCl$ 265.1233, 267.1204; found 265.1230, 267.1208.

**Supplementary Material Available:** A listing of properties and full spectral data of compounds **1b–e, 2b–e, 3b, 3d,e, 5, 10–13, 15a–c, 16a–c, 16d** (X = Br, I), **17a, 17c, 17d** (X = Br), **20, 22–24, 33,** and **34** and the preparation of the authentic sample of **27** (11 pages). Ordering information is given on any current masthead page.

# Unusual Reactions between 1,4-Dihydropyridines and 1,2,4,5-Tetrazines in the Presence of K-10/Fe(III) Clay Catalyst

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Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates **1a–c** add to 3,6-dipyridyl-1,2,4,5-tetrazines **2a–c** according to two different routes, neither of which is the anticipated inverse electron demand Diels–Alder reaction with **1** as dienophile and **2** as diene. The first route is followed by NH compounds **1a–c**; they undergo a "hydrogen-transfer" reaction which can be catalyzed by K-10/Fe(III) clay. *N*-Methyl-1,4-dihydropyridine **1d** undergoes a different dehydrogenation, leading to 2-methylene-1,2-dihydropyridine derivative **7**, which, in turn, adds to **2** with nitrogen loss, leading to a spiro bicyclic intermediate **8**, whose aromatization gives the open-chain pyridazines **5a–c**. These are easily converted into their cyclized counterpart (**6a–c**) with the attendant loss of ethanol.

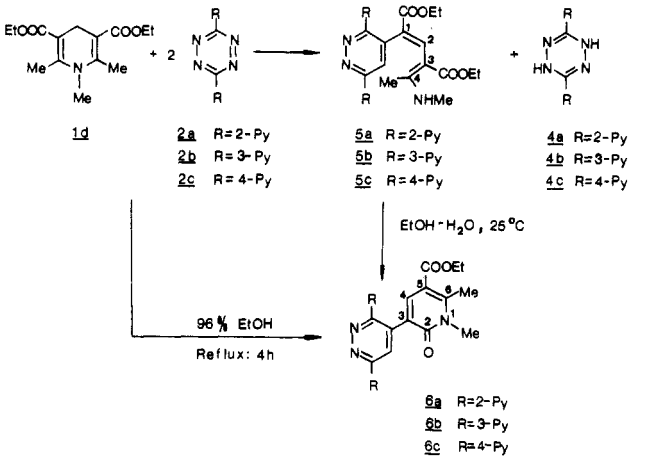
Catalysis of organic reactions by inorganic solids often allows one to run reactions at ambient temperature and pressure, with high yields and selectivities.[1] We have shown that 1,4-dihydropyridines can be aromatized efficiently in the presence of clay catalysts.[2] Some heterocyclic systems, when submitted to the nitrating reagent "clayfen",[3] give rise to quite interesting products.[4] We report here somewhat unexpected reaction pathways, some of which are catalyzed by the modified K-10 montmorillonite exchanged with ferric ions.

Our initial plan was to perform a Diels–Alder reaction, since diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**) can serve as a dienophile in a [4 + 2] cycloaddition involving a hetero diene as the reaction partner.[5] For this latter role, we chose 1,2,4,5-tetrazines, which are known to be excellent dienes in inverse electron demand Diels–Alder reactions.[6] They have been shown to participate in Diels–Alder reactions with a number of olefinic and acetylenic dienophiles to produce 1,4-dihydropyridazines, 4,5-dihydropyridazines, and pyridazines.[6] Only a limited group of nitrogen-containing heterocyclic compounds, such as 1-methylpyrrole,[7] 1-methylimidazole, and indole[8] have been used as dienophiles in such cycloadditions.

We report here our first results on the reactions of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates **1a–d**[9-12] with 3,6-dipyridyl-1,2,4,5-tetrazines **2a–c**.[13,14] A first unexpected finding was that compounds **1a–c** ($R^2$ = H), instead of the anticipated Diels–Alder reaction, undergo a "hydrogen-transfer" reaction converting them into the corresponding pyridines (**3a–c**), the tetrazine **2** serving as the acceptor of an hydrogen molecule (details in the supplementary material).

This facile oxidation route is subject to catalysis by the acidic K-10 montmorillonite doped with ferric ions according to the standard procedure.[15] We had already reported its use for catalysis of Diels–Alder reactions.[16,17] Here this catalyst appears to speed up the reaction of the

**Scheme I**

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(1) Laszlo, P. *Acc. Chem. Res.* **1986**, *19*, 121.
(2) Balogh, M.; Hermecz, I.; Mészáros, Z.; Laszlo, P. *Helv. Chim. Acta* **1984**, *67*, 2270.
(3) Cornélis, A.; Laszlo, P. *Synthesis* **1985**, 909.
(4) Balogh, M.; Hermecz, I.; Mészáros, Z.; Laszlo, P. Presented at the Conference of the Hungarian Academy of Sciences on Heterocyclic Chemistry, Balatonfüred, Hungary, 1985.
(5) Balogh, M.; Hermecz, I.; Náray-Szabó, G.; Simon, K.; Mészáros, Z. *J. Chem. Soc., Perkin Trans. 1* 1986, 753.
(6) For a review of Diels–Alder reactions of 1,2,4,5-tetrazines, see: Boger, D. L. *Tetrahedron*, **1983**, *39*, 2869. See also: Seitz, G.; Overhen, W. *Arch. Pharm. (Weinheim)* **1977**, *310*, 936, 1023; **1979**, *312*, 452. Figeys, H. P.; Mathy, A.; Dralants, A. *Synth. Commun.* **1981**, *11*, 655.
(7) (a) Seitz, G.; Kämpchen, T. *Chem. Ztg.* **1975**, *99*, 292. (b) Seitz, G.; Kämpchen, T. *Arch. Pharm. (Weinheim)* **1976**, *309*, 679.
(8) Takakashi, M.; Ishida, H.; Kahmato, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1725.
(9) Checchi, S. *Gazz. Chim. Ital.* **1959**, *89*, 2151.
(10) Traber, W.; Karrer, P. *Helv. Chim. Acta* **1958**, *41*, 2066.
(11) Loev, B.; Snader, K. M. *J. Org. Chem.* **1965**, *30*, 1914.
(12) Brignell, P. J.; Eisner, U.; Farrell, P. G. *J. Chem. Soc. B* **1966**, *11*, 1083.

0022-3263/87/1952-2026$01.50/0 

**Table I. Reaction Conditions, Yields, and Melting Points of Products from Reactions of Compound 1d with 2a–c**

| | reaction conditions | | | | reaction products | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 5 | | 4 | | |
| | solvent | temp, °C | catalyst | time, h | | yield, %[a] | | yield, %[b] | mp, °C |
| **2a**[13] | Toluene | 110 | | 1 | **5a** | 92[c] | **4a** | 49 | 192–195[d] |
| **2a** | $CH_2Cl_2$ | 25 | | 24 | **5a** | 75[e] | **4a** | 43 | 192–194 |
| **2a** | $CH_2Cl_2$ | 25 | K-10/Fe(III) | 10 | **5a** | 78 | **4a** | 45 | 186–188[f] |
| **2b**[14] | Toluene | 110 | | 1 | **5b** | 73 | **4b** | 44 | 228–231[g] |
| **2b** | $CH_2Cl_2$ | 25 | | 24 | **5b** | 54[c] | **4b** | 38 | 228–230 |
| **2b** | $CH_2Cl_2$ | 25 | K-10/Fe(III) | 10 | **5b** | 79 | **4b** | 28 | 214–216[f] |
| **2c**[14] | Toluene | 110 | | 1.5 | **5c** | 88[e] | **4c** | 49 | 273[h] |
| **2c** | $CH_2Cl_2$ | 25 | | 25 | **5c** | 76[e] | **4c** | 47 | 272–273 |
| **2c** | $CH_2Cl_2$ | 25 | K-10/Fe(III) | 12 | **5c** | 91 | **4c** | *i* | |

[a] Yields are calculated on the basis of **1d**. [b] Yields are calculated on the basis of **2a–c**. [c] Column chromatography with benzene/MeOH (100:1). [d] Lit. mp 197–198 °C.[13] [e] Column chromatography with $CHCl_3$/MeOH (100:1). [f] A mixture of **4a** and **2a** was isolated, because **4a** can be aromatized partially in the presence of K-10/Fe(III) catalyst. [g] Lit. mp 235 °C.[14] [h] Lit. mp 272 °C.[14] [i] **4c** was filtered off together with the clay because of its low solubility in $CH_2Cl_2$.

parent molecule (**1a**), while its presence is essential to the success of the reaction from the 4-substituted compounds **1b,c** (Table I). These 1,4-dihydropyridine systems have been used recently as mimetic enzymes for their resemblance with the NADH system.[18] It is interesting that reduction of numerous unsaturated compounds by 1,4-dihydropyridines is subject to catalysis by silica gel[18] and also by divalent cations such as Ni(II), Co(II), Zn(II), Mn(II), and Mg(II).[19] A clay system such as used here provides both the advantages of adsorption onto a solid surface with the attendant increase in encounter rates of reactants stemming from the reduction in dimensionality[1] and the advantageous presence of Fe(III) Lewis acidic centers in abundance (together with that of other cationic centers in lesser amounts). To the best of our knowledge, this is the first report of catalysis by such a clay system of the redox reaction **1** → **3**. Clearly, the intended use of dihydropyridines **1** as electron-rich dienophile partners of inverse electron demand Diels–Alder reactions with the electron-deficient 3,6-diaryl-1,2,4,5-tetrazines **2** suffers from the lack of nucleophilic character in the dienophile. These dihydropyridines **1** are readily oxidized molecules, the 1,2,4,5-tetrazines **2** are well-recognized oxidants, hence the redox reaction that prevails between them.

A second unexpected observaton came when we treated 1-methyl-1,4-dihydropyridine (**1d**) with tetraazines **2a–c**. Again we could isolate the dihydrotetrazines **4a–c**, and it is remarkable that the K10/Fe(III) does not stoichiometrically reoxidize them, but they were accompanied by bright yellow products (**5a–c**) (Scheme I). The structural identification of these products is based on the elemental formula $C_{26}H_{27}N_5O_4$, as given by the microanalysis and by the mass spectrometric data. The other spectral data, IR, UV, and $^1H$ and $^{13}C$ NMR agree nicely with the proposed structures **5a–c**. Noteworthy was the better quality (narrower lines) of the $^1H$ NMR spectrum for **5a** when obtained on a spectrometer at 60 or 80 MHz as compared with one at 300 MHz. Conceivably, this artifact is due to small nonequivalences which are partially resolved at 300 MHz and are not visible at 60 or 80 MHz. Molecule **5a** also distinguishes itself by the downfield shift of H5 by 0.9 ppm (Table IV, supplementary material) matched by that of C5 and even more by the 6 ppm downfield shift of C4 when compared with **5b,c**. We do not have enough evidence at present to offer an explanation, and we plan to investigate further these interesting effects.

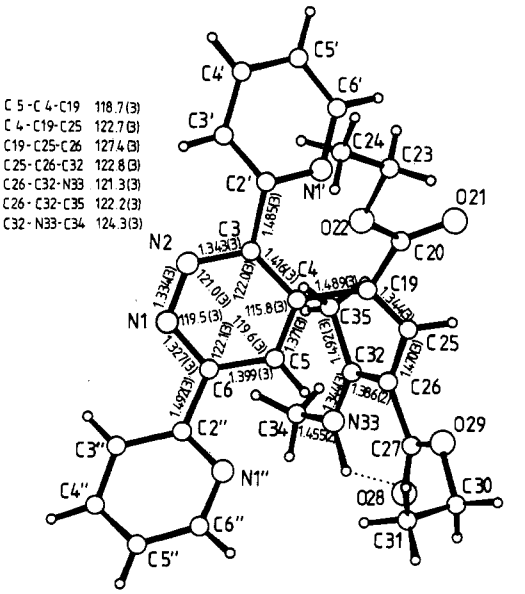
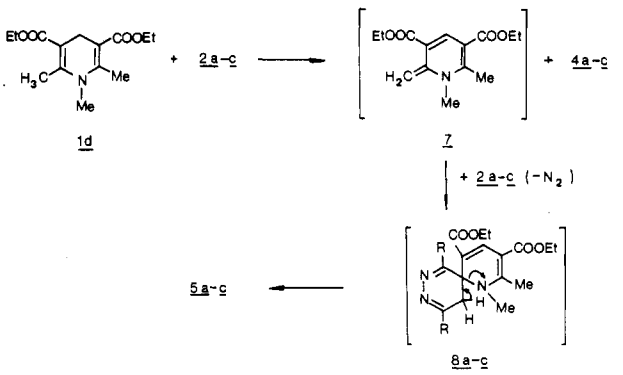



**Figure 1.** X-ray molecular diagram of compound **5a** with crystallographic atomic numbering. Selected bond lengths and bond angles are given (esd's in parentheses).

**Scheme II**




Structure **5** was confirmed by X-ray crystallography (Figure 1). As befits such a rather congested structure, some distortions occur in order to relieve steric strain: for instance, the angle at trigonal C25 opens to 127.4°, and the six-membered rings are somewhat tilted to each other,

(13) Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318.
(14) Dallacker, F. *Monatsch. Chem.* **1960**, *91*, 294.
(15) K-10/Fe(III) catalyst was prepared according to published procudures: Tennakoon, D. T. B.; Thomas, J. M.; Tricker, M. J.; Williams, J. D. *J. Chem. Soc. Dalton Trans.* **1974**, 2207.
(16) Laszlo, P.; Lucchetti, J. *Tetrahedron Lett.* **1984**, *25*, 1567.
(17) Laszlo, P.; Lucchetti, J. *Tetrahedron Lett.* **1984**, *25*, 2147.
(18) Nakamura, K.; Fuji, M.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1984**, *25*, 3983.
(19) Reviews of dihydropyridine chemistry: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.

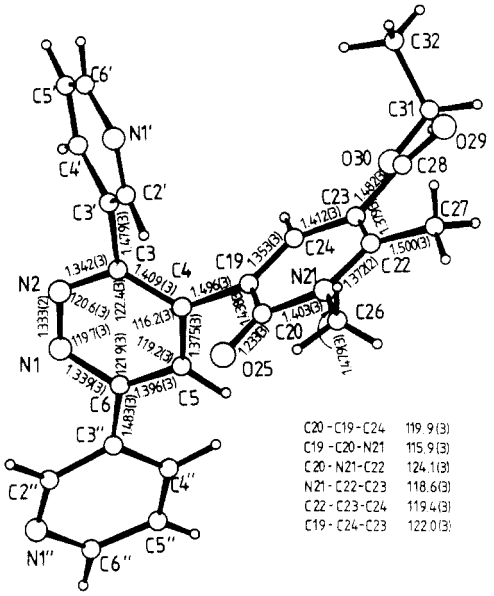



**Figure 2.** X-ray molecular diagram of compound **6b** with crystallographic atomic numbering. Selected bond lengths and bond angles are given (esd's in parentheses).

probably due to the large substituent at C4.[20] It is interesting to note also that the 1,3-butadiene part of the molecule adopts an s-cis rather than an s-trans conformation. This could be due to crystal packing forces favoring a more compact against a more extended conformation, or it could be due to secondary orbital interactions.

Molecules **5a–c** are easily cyclized to 2-oxo-1,2-dihydropyridine derivatives **6a–c** by treatment with 50% aqueous ethanol at ambient temperature (Scheme I). X-ray crystallographic analysis of **6b** shows that the formation of the new ring causes a more significant twist around C3–C3′ and C6–C3″ bonds[21] (Figure 2).

We find that the optimum molar ratio for the cycloaddition reaction initiating the second pathway (Scheme I) is 1 mol of **1d** for 2 mol of **2a–c**. Accordingly, we conjecture the mechanism depicted in Scheme II: it might start with an unusual "hydrogen transfer" in which the tetrazine (**2a–c**) abstracts an hydrogen from C4 and from the methyl group at C2, leading presumably to diethyl 1,6-dimethyl-2-methylene-1,2-dihydropyridine-3,5-dicarboxylate (**7**).[22] This intermediate **7** would then be trapped into [4 + 2] cycloaddition with the second molecule of the tetrazine, acting as dienophile, and with extrusion of dinitrogen. This step would result in spiro compound **8**, in which the 4,5-dihydropyridazine moiety aromatizes by prototropic tautomerism and opening of the pyridine ring (Scheme II).

We have prepared intermediate **7** independently by Mumm's method,[22] and we have checked that this 2-methylene compound reacts readily in refluxing toluene with one molecule of tetrazine (**2**) to yield the open-chair compound **5**.

In summary, the most interesting feature is what the two pathways reported here have in common. They both start with a dehydrogenation effected by the tetrazine. This dehydrogenation is the familiar one, that with biomimetic value, in the first pathway. When it is blocked by the presence of an *N*-methyl group, then the second hydrogen is taken from the C2-methyl group (Scheme II). It will be of interest to determine if the hydrogens at C4 and on C2-methyl are removed stepwise or in a synchronous manner.

On the practical side, the reactions presented here offer a simple and attractive access to systems of the type of **5** and **6**. In the latter case readily available 1,4-dihydropyridines can be transformed, almost in one pot, into highly functionalized 3-aryl-2-pyridones.

## Experimental Section

All melting points are uncorrected. UV spectra were obtained in ethanol on a UNICAM SP 800 spectrometer. IR spectra were determined with KBr disks on a ZEISS UR 20 spectrophotometer. The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ with Varian EM 360L 60-MHz, Bruker WP-80 DS, and Bruker AM-300 MHz spectrometers. Chemical Shifts were determined on the$\delta$ scale, with tetramethylsilane ($\delta = 0$) as internal standard. Mass spectra were measured with an MS-902 spectrometer operating at 70 eV. The progress of the reactions was monitored by TLC [silica gel 60 $F_{254}$, Merck, benzene/MeOH (4:1)]. Silica gel 60 (Merck, 70–230 mesh ASTM) was used for column chromatography.

**"Hydrogen-Transfer" Reaction between Diethyl 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylates 1a–c and 3,6-Di-2-pyridyl-1,2,4,5-tetrazine (2a). General Procedure.** (a) 1,4-Dihydropyridines **1a–c** (1 mmol) and 1,2,4,5-tetrazine **2a**[13] (0.236 g, 1 mmol) were dissolved in 25 mL of solvent. The mixture was stirred (for the solvent, temperature, and reaction time, see Table I), supplementary material). The orange solution was evaporated to dryness and treated with ethyl acetate (3 mL). The insoluble 3,6-di-2-pyridyl-1,2-dihydro-1,2,4,5-tetrazine (**4a**) was filtered off and washed with ether (1 mL). From the filtrate the pure diethyl 2,6-dimethylpridine-3,5-dicarboxylates **3a–c** were isolated after evaporating the solvent. Yields and melting points are given in Table I of the supplementary material.

(b) A mixture of **1a–c** (1 mmol), **2a** (0.236 g, 1 mmol), K-10/Fe(III)[15] (0.55 g) or K-10 clay (0.55 g), and $CH_2Cl_2$ (25 mL) was stirred at 25 °C. (Reaction times are given in Table I of the supplementary material.) When the reaction was complete, the clay was filtered off and washed with $CH_2Cl_2$ (15 mL). The filtrate was evaporated to dryness and workup was the same as above.

**Preparation of Diethyl 4-(Methylamino)-1-(3,6-dipyridyl-4-pyridazinyl)-1,3-pentadiene-1,3-dicarboxylates 5a–c. General Procedure (Scheme I).** (a) *N*-Methyl-1,4-dihydropyridine **1d** (0.535 g, 2 mmol) and tetrazine **2a–c** (0.945 g, 4 mmol) were dissolved in toluene (40 mL) or in $CH_2Cl_2$ (80 mL). The mixture was stirred for several hours. (For the temperature and reaction time see Table I.) After the disappearance of the red color of the tetrazines, the solvent was evaporated, and the orange residue was treated with ethyl acetate (5–10 mL) to isolate the 1,2-dihydrotetrazine **4a–c**. The filtrate was evaporated and purified by column chromatography using benzene/MeOH (100:1) or $CHCl_3$/MeOH (100:1) solvent mixture as eluent. The open-chain compounds **5a–c** were isolated as bright yellow oils, which solidified after treating with ether.

(b) A mixture of **1d** (2 mmol), tetrazine **2a–c** (4 mmol), K-10/Fe(III) catalyst (1.15 g), and $CH_2Cl_2$ (80 mL) was stirred at 25 °C for 10–12 h, and then the clay was filtered off and washed with $CH_2Cl_2$ (15 mL). Workup was the same as above. Yields

(20) The conformation of **5a** can be described by five planes. P1: N1, N2, C3, C4, C5. P2: N1′, C2′, C3′, C4′, C5′. P3: N1″, C2″, C3″, C4″, C5″. P4: C4, C19, C20, O21, O22, C23, C24, C25. P5: C25, C26, C27, O28, O29, C32, N33, C34, C35. In each plane the maximum deviation is less than 0.1 Å. Dihedral angles between least-squares planes: P1,P2, 26°; P1,P3, 20°; P1,P4, 65°; P4,P5, 80°. The delocalized bond systems in the molecule are separated by the C4–C19 (1.489 Å) and by the C25–C26 (1.470 Å) bonds. The enamine double bond (C26–C32, 1.386 Å) is delocalized toward N33 (C32–N33, 1.344 Å). The N33–H···O28 intramolecular hydrogen bond stabilizes the planarity of this moiety [X···Y, 2.678 Å; H···Y, 1.889 Å; X–H···Y, 126°].

(21) The conformation of **6b** can be described by four planes. P1: N1, N2, C3, C4, C5. P2: N1′, C2′, C3′, C4′, C5′. P3: N1″, C2″, C3″, C4″, C5″. P4: C19, C20, N21, C22, C23, C24, C4, C26, C27, C28. The maximum deviation in each plane is less than 0.05 Å. The dihedral angles between the least-squares planes: P1, P, 51°; P1,P3, -31°; P1, P4, 87°. There is a delocalized bond system in each ring; the C19–C20 bond is the longest among the endocyclic bonds (1.438 Å).

(22) Mumm, O.; Behrens, K.; Fisher-Treuenfeld, V. A.; Hingst, G.; Lund, W.; Mrozek, O.; Sönksen, J.; Tonn, O. *Justus Liebigs Ann. Chem.* **1925**, *443*, 272.

(23) Kamal, A.; Ahmad, M.; Mohd, N.; Hamid, A. M. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 610.

and melting points are summarized in Table I.

**5a** (R = 2-pyridyl): mp 132–134 °C (ether); mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 65.63; H, 5.94; N, 14.89. $\lambda_{max}$ 380 (infl.), 330 (infl.), 289 (log $\epsilon$ 4.59), 249 nm (4.33); $\nu_{max}$ 3270 (NH), 1710, 1700 (C=O)8 1640 $cm^{-1}$ (C=C).

**5b** (R = 3-pyridyl): mp 102–104 °C (ether); mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 66.12; H, 5.98; N, 14.62. $\lambda_{max}$ 382 (log $\epsilon$ 4.07), 326 (4.14), 278 (4.47), 250 nm (infl.); $\nu_{max}$ 3250 (NH), 1700 (C=O), 1655 $cm^{-1}$ (C=C).

**5c** (R = 4-pyridyl): mp 169–170 °C; mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 66.06; H, 5.68; N, 14.90. $\lambda_{max}$ 380 (infl.) 326 (log $\epsilon$ 4.04), 266 nm (4.36); $\nu_{max}$ 3260 (NH), 1700 (C=O), 1645 $cm^{-1}$ (C=C).

**Preparation of Ethyl 1,6-Dimethyl-2-oxo-3-(3,6-dipyridyl-4-pyridazinyl)-1,2-dihydropyridine-5-carboxylates 6a–c.** (a) **5a–c** (0.473 g, 1 mmol) were dissolved in 5–10 mL of ethanol. Water (5–10 mL) was added to the yellow solution, and the mixture was stirred at 25 °C for 5–6 h. The yellow color disappeared and white crystals separated, 2-Oxo-1,2-dihydropyridines **6a–c** were filtered off and washed with water.

**6a** (R = 2-pyridyl): yield, 0.376 g (88%); mp 210–211 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.19; H, 5.06; N, 16.19. $\lambda_{max}$ 330 (infl.), 280 (log $\epsilon$ 4.58), 250 nm (infl.); $\nu_{max}$ 1710 (C=O, ester), 1660 $cm^{-1}$ (C=O, ring).

**6b** (R = 3-pyridyl): yield, 0.316 g (74%); mp 204–205 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.11; H, 5.13; N, 16.28. $\lambda_{max}$ 332 (log $\epsilon$ 3.99), 270 nm (4.50); $\nu_{max}$ 1708 (C=O, ester), 1665 $cm^{-1}$ (infl. C=O, ring).

**6c** (R = 4-pyridyl): yield, 0.324 g (76%); mp 240–241 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.25; H, 5.16; N, 16.31. $\lambda_{max}$ 336 (log $\epsilon$ 3.94), 262 (4.53), 236 nm (infl.); $\nu_{max}$ 1710 (C=O, ester), 1659 $cm^{-1}$ (C=O, ring).

(b) A mixture of **1d** (1.069 g, 4 mmol), **2a–c** (1.889 g, 8 mmol), and 100 mL of 96% EtOH was stirred at reflux temperature for 4 h. The solvent was removed with a rotary evaporator, then $CHCl_3$ (10 mL) was added, and the insoluble 1,2-dihydrotetrazine **4a–c** was filtered off. The filtrate was evaporated to dryness, the residue was recrystallized from EtOH to give 2-oxo-1,2-dihydropyridines **6a–c** in 56%, 78%, and 64% yields: mp 210–211, 204–206, and 240–241 °C, respectively.

**Preparation of Diethyl 4-(Methylamino)-1-[3,6-di-2-pyridyl-4-pyridazinyl]-1,3-pentadiene-1,3-dicarboxylate (5a) from Diethyl 1,6-Dimethyl-2-methylene-1,2-dihydropyridine-3,5-dicarboxylate (7). 3a** (2.51 g, 10 mmol) and 1.75 mL of dimethyl sulfate were stirred at 60 °C for 6 h. 1,2,6-Trimethylpyridinium methylsulfate was extracted with ether (4 × 15 mL) to remove the excess of dimethyl sulfate and then was dissolved in water (10 mL). $Na_2CO_3$ (3.39 g, 32 mmol) was added, and the mixture was stirred at 25 °C for 5 min, extracted with $CHCl_3$ (3 × 30 mL), dried over $MgSO_4$, and evaporated to dryness. 2-Methylene compound **7** was isolated as red oil (2.62 g, 98.1%). **7** and tetrazine **2a** (2.24 g, 9,5 mmol) were dissolved in toluene (100 mL) and were refluxed for 45 min. Toluene was removed by a rotary evaporator, and the residue was purified by column chromatography using ethyl acetate as eluent. **5a** (2.60 g, 56%) was isolated as yellow solid: mp 134–135 °C (from ether).

**Crystallography. Crystal data for 5a**: $C_{26}H_{27}N_5O_4$, for = 473.54; triclinic; $a$ = 10.655 (1) Å, $b$ = 11.042 (1) Å, $c$ = 11.751 (3) Å; $\alpha$ = 64.02 (2)°, $\beta$ = 83.57 (2)°, $\gamma$ = 81.02 (2)°; $D_{calcd}$ = 1.202 g $cm^{-3}$; $Z$ = 2; crystal size 0.3 × 0.4 × 0.5 mm; space group $P\bar{1}$; $\lambda$(Cu K$\bar{\alpha}$ = 1.5418 Å). Data were collected on an automated four-circled Enraf-Nonius CAD-4 diffractometer with monochromated Cu K$\bar{\alpha}$ radiation ($\theta_{range}$ 1.5–75.0°): $N_{tot}$ 5046; $N_R$ 4304 [$I > 3\sigma(I)$]; $N_{par}$ 317 + 108. The initial structure model was developed by direct method[24] (MULTAN 83) applied for 450 $E$ values and included all 35 non-H atoms. After anisotropic full-matrix refinement for the non-hydrogen atoms the hydrogen atoms were obtained from difference electron-density (e.d.) synthesis, and their parameters were refined isotropically before the final anisotropic refinement for the non-hydrogen atoms ($R_R$ = 0.054, $R_w$ = 0.088). The final $\Delta F$ map contained features ranging from 0.25 to 0.30 e/Å$^3$.

**Crystal data for 6b**: $C_{24}H_{21}N_5O_3$, fw = 427.47; monoclinic; $a$ = 18.497 (1) Å, $b$ = 5.880 (2) Å, $c$ = 19.228 (2) Å; $\beta$ = 104.82 (2)°; $D_{calcd}$ = 1.404 g $cm^{-3}$; $Z$ = 4; crystal size 0.1 × 0.1 × 0.4 mm; space group $P2_1/c$; $\lambda$(Cu K$\bar{\alpha}$ = 1.5418 Å). Data were collected and processed much the same way as for **5a**, including structure solution and refinement: $\theta_{range}$ 1.5–75.0°; $N_{tot}$ 4171; $N_R$ 2296 [$I > 3\sigma(I)$]; $N_{par}$ 290 + 84; $R_R$ = 0.040; $R_w$ = 0.039. The final $\Delta F$ map contained peaks ranging from 0.20 to 0.26 e/Å$^3$.

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**Supplementary Material Available:** Characteristics of the redox reactions 1 + 2, $^{13}C$ NMR chemical shifts for compounds **5a–c** and **6a–c**, and bond lengths, bond angles, torsion angles, and relative atomic coordinates for **5a** and **6b** (9 pages). Ordering information is given on any current masthead page.

(24) Fan, H.; Yao, J.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *A39*, 566.

# Total Synthesis of (±)-5-*O*-Methyllicoricidin

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A novel intramolecular Mitsunobu alkylation is employed to construct the benzopyran moiety of the newly isolated isoflavan 5-*O*-methyllicoricidin. This convergent 15-step total synthesis outlines a chemically mild approach to the acid-sensitive isoflavanoids.

For centuries the dried rhizomes and roots of the genus *Glycyrrhiza* (Leguminosae) have been used in both Asia and Europe as a herbal remedy for respiratory and peptic ailments. A principal isoflavandiol ingredient was isolated

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