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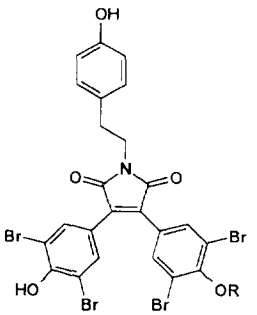
# Biomimetic Total Synthesis of Polycitrin A

**Andreas Terpin, Kurt Polborn and Wolfgang Steglich***

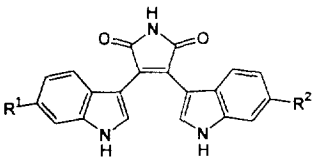
Institut für Organische Chemie der Universität, Karlstraße 23, D-80333 München, Germany

**Abstract**: The synthesis of the marine alkaloid polycitrin A (**1a**) is described. The synthesis is based on the formation of 3,4-bisarylpyrrole-2,5-dicarboxylic acids from 3-arylpyruvic acids by oxidative coupling and consecutive pyrrole ring formation. The pyrrole dicarboxylic acids are then converted into 3,4-bisaryl maleimides by treatment with hypochlorite. The synthesis is completed by bromination and introduction of the *N*-alkyl substituent. **1a** is thus obtained in 6 steps from 3-(4-methoxyphenyl)pyruvic acid (**6**) with 26% overall yield.

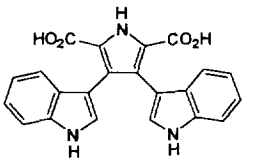
Recently, Kashman and coworkers[1] reported the isolation and structural elucidation of the alkaloids polycitrin A (**1a**) and B (**1b**) from a *Polycitor* species (Ascidiaceae). The polycitrins show a close structural resemblance to the slime mould metabolites arcyriarubin A-C (**2a-c**)[2]. Both types of alkaloids contain a maleimide unit with two aromatic residues at positions 3 and 4. In addition, the nitrogen of the marine metabolites is substituted with a (4-hydroxyphenyl)ethyl residue.




| | R |
|---|---|
| **1a** | H |
| **1b** | $CH_3$ |




| | $R^1$ | $R^2$ |
|---|---|---|
| **2a** | H | H |
| **2b** | OH | H |
| **2c** | OH | OH |

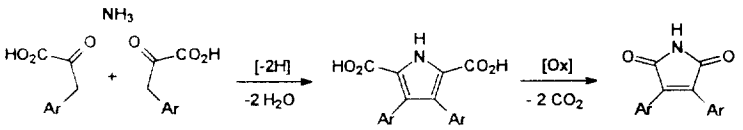



**3a**

We reasoned that both types of maleimides **1** and **2** could be derived biogenetically by oxidative degradation from the corresponding 3,4-bisaryl-pyrrole-2,5-dicarboxylic acids, formed in turn by oxidative

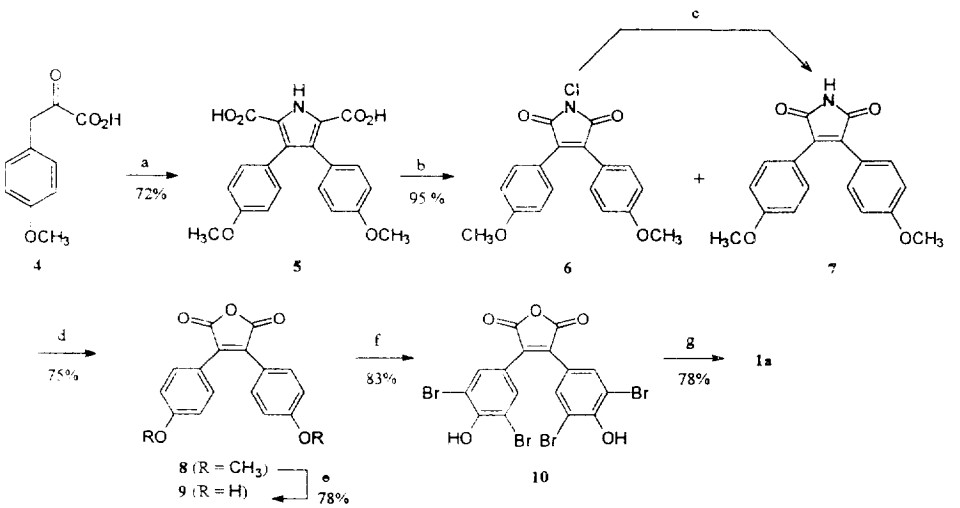
dimerization of the corresponding arylpyruvic acid and consecutive closure of the pyrrole ring with ammonia[3] (Scheme 1). This idea is supported by the co-occurrence of arcyriarubin A (**2a**) with lycogalic acid A (**3a**) in the slime mould *Lycogala epidendrum*[3].

Scheme 1



We used this approach for a short synthesis of polycitrin A (**1a**) (Scheme 2). Treatment of the dianion derived from 3-(4-methoxyphenyl)pyruvic acid (**4**) and *n*-BuLi in THF at -78 °C with iodine followed by reaction of the resulting solution with ammonia and $TiCl_4$ at room temperature afforded 3,4-bis (4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid (**5**) in 72% yield. On oxidation with an aqueous sodium hypochlorite solution pyrrole dicarboxylic acid **5** was transformed into a mixture of maleimide **7** and the corresponding *N*-chloro derivative **6**. To avoid rearrangement of the *N*-chloroamide into the 2*H*-1,3-oxazin-2,6-dione[4], the reaction mixture was quenched with aqueous sodium hydrogensulfite. By means of this procedure maleimide **6**

Scheme 2



**Reagents**: (a) (i) THF, n-BuLi, -78 °C, (ii) 0.5 eq. $I_2$, -78 °C → 25 °C, (iii) $NH_3$, $TiCl_4$; (b) NaOCl; (c) $NaHSO_3$; (d) (i) KOH, (ii) HCl; (e) $BBr_3$; (f) $Br_2$, AcOH; (g) tyramine, diisopropylethylamine, PhOH (melt), 160 °C.

can be obtained in 95% yield. Hydrolysis of **7** provided anhydride **8** which after conversion into the free phenol **9** was brominated to the tetrabromo derivative **10**. Subsequent heating of **10** with tyramine and Hünig's base in phenol afforded polycitrin A (**1a**) as red, fluorescent crystals, mp 180-181 °C.

**1a** can thus be obtained in 6 steps from 3-(4-methoxyphenyl)pyruvic acid (**4**) in 26% overall yield. The spectral data of the synthetic compound corresponded well to those of the natural product which, however, has been described as an oil[1]. Structure **1a** was confirmed by X-ray analysis (Figure 1) indicating a strong out of plane distortion (53 deg) of the two phenyl rings.

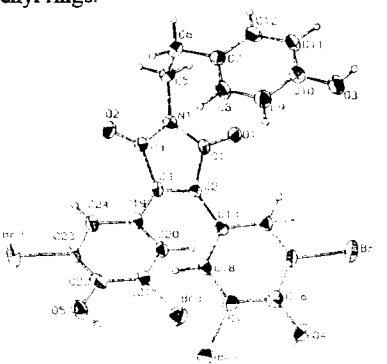


Figure 1. Molecular structure of polycitrin A (**1a**)

## Experimental

**General**. All solvents were distilled before use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl under argon prior to use. *n*-Butyllithium was purchased from Acros. The reactions were monitored by TLC and/or $^1$H NMR prior to work-up. Solvents were evaporated from the reaction mixtures a $\leq$ 40°C with a rotavapor. TLC was run on silica plates 60 $F_{254}$ (Merck) and visualized with UV fluorescence (254 and 366 nm). Flash chromatography was performed on $SiO_2$ 60, 0.063 - 0.200 mm (Merck).

M. ps. were determined on a micro hot stage apparatus (Reichert Thermovar) and are uncorrected. IR spectra were recorded on a Bruker IFS 45 FT-IR. UV spectra on a Hewlett Packard 8452 diode array spectrometer. $^1$H and $^{13}$C NMR spectra were measured on Bruker AMX 300, AMX 600 and Varian VXR 400 S instruments. Chemical shifts are given as $\delta$ values from internal TMS. The mass spectra were recorded on Finnigan MAT 90 and MAT 95 Q instruments. The X-ray diffraction analysis was carried out on a Enraf-Nonius CAD4 diffractometer at room temperature [296(2) K] using Mo $K_\alpha$ ($\lambda$ = 0.71073 Å) radiation.

3-(4-Methoxyphenyl)pyruvic acid (**4**) was prepared from anisaldehyde *via* the azlactone route[5] and was dried *in vacuo* before use.

**3,4-Bis(4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid (5)**

*n*-BuLi (10.3 ml of a 2.5 M solution in hexanes, 25.75 mmol, 2.0 eq.) was added dropwise to a stirred solution of 3-(4-methoxyphenyl)pyruvic acid (**4**) (2.5 g, 12.9 mmol, 1.0 eq.) in dry THF (120 ml) at -78°C. The resulting white suspension of the monoanion dissolved after addition of the second half of base under formation of the yellow dianion. After stirring the mixture for 25 min a solution of iodine (1.63 g, 6.45 mmol, 0.5 eq.) in anhydrous THF (20 ml) was added dropwise. The mixture was allowed to warm up to 25 °C and a slow stream of $NH_3$ was passed in for 10 min. After saturation of the solution with $NH_3$, $TiCl_4$ (0.71 ml, 6.43 mmol, 0.5 eq.) in hexanes (20 ml) was added and the resulting brown suspension was stirred for 24 h whereby it changed to light yellow. The reaction was quenched with 0.2 N NaOH (150 ml) and the aqueous layer washed with ethyl acetate (2 x 50 ml). The pH was adjusted to 4 by addition of conc. HCl, and the aqueous phase was extracted with ethyl acetate (4 x 150 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield 1.90 g of crude material. Rinsing the product with precooled methanol (1 ml) gave **5** as colourless crystals (1.70 g, 72%); mp 268-270 °C. - UV ($CHCl_3$): $\lambda_{max}$ ($\varepsilon$) = 258 nm (17640). - IR (KBr): $\tilde{\nu}$ = 3515 (m), 3400 (w), 3010 (w), 2945 (w), 2828 (w), 1732 (s), 1680 (s), 1564 (m), 1487 (s), 1473 (s), 1409 (m), 1376 (w), 1292 (w), 1239 (m), 1188 (m), 1085 (w), 1033 (w), 956 (m), 832 $cm^{-1}$ (w). - $^1H$ NMR ([$D_6$]DMSO, 300 MHz): $\delta$ 3.69 (s, 6H, 2 $OCH_3$), 6.72 (d, $J$ = 8.3 Hz, 4H), 6.95 (d, $J$ = 8.3 Hz, 4H), 11.58 (s, 1H, NH), 12.55 (s, br., 2H, $CO_2H$). - $^{13}C$ NMR ([$D_6$]DMSO): $\delta$ = 55.02 (Ph-$OCH_3$), 112.79 (CH), 122.23, 126.20, 129.93 (all quart. C), 131.96 (CH), 157.93 (C-$OCH_3$), 161.64 ($CO_2R$). - FAB-MS: *m/z* (rel. intensity) 391 (4) $[M+H+Na]^+$, 368 (31) $[M+H]^+$, 367 (52) $[M]^+$, 350 (9) $[M-OH]^+$, 307 (58) $[M-CH_3-CO]^+$, 289 (24), 154 (100), 136 (60). - $C_{20}H_{17}NO_6$ (MW 367.36). Calc.: C 65.39, H 4.66, N 3.81%. Found: C 65.38, H 4.69, N 3.78%.

**3,4-Bis(4-methoxyphenyl)maleimide (7)**

A suspension of **5** (1.0 g, 2.7 mmol) in ethyl acetate (250 ml) was refluxed until a clear solution resulted. On addition of aqueous NaOCl solution (10 ml, 13% active chlorine, excess) with stirring the reaction mixture immediately turned yellow. After additional stirring for 10 min without heating, the layers were separated. The organic phase was treated with a mixture of dioxane (100 ml) and aqueous $NaHSO_3$ solution (100 ml, 10%) and stirred for 12 h at 25 °C. After separation of the layers the aqueous phase was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (0.9 g) was purified by flash column chromatography (petrol ether-ethyl acetate 1:1) to afford **7** (0.80 g, 95 %); mp 241-242 °C. - UV ($CH_3OH$): $\lambda_{max}$ = 206 (16563), 232 (16449), 330 (4320), 396 nm (6094). - IR (KBr): $\tilde{\nu}$ = 3400 (w, br), 3192 (m, br), 3070 (m), 2970 (w), 2840 (w), 1761 (s), 1707 (s), 1603 (s), 1560 (w), 1517 (s), 1504 (s), 1463 (m), 1440 (m), 1425 (w), 1345 (s), 1303 (s), 1290 (s), 1258 (s), 1181 (s), 1177 (w), 1145 (w), 1115 (w), 1027 (m), 1016 (s), 1005 (m), 950 (w), 860 (w), 842 (m), 825 (m), 798 (m), 755 (m), 725 (w), 665 (w), 630 (w), 620 (w), 580 (m), 560 (m), 528 (m), 520 (m), 500 (w), 450 (w) $cm^{-1}$. - $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.81 (s, 6H, 2 x $OCH_3$), 6.86 (d, $J$ = 8.9 Hz, 4H), 7.36 (s, NH), 7.45 (d, $J$ = 8.9 Hz, 4H). - $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 55.30 (Ph-$OCH_3$), 114.15 (quart. C), 121.03 (quart. C), 131.43 (CH), 134.97 (quart. C), 160.82 (C-$OCH_3$), 170.72 (CO). - EI MS (180°C): *m/z* (rel. intensity) 310 (17) $[MH^+]$, 309 (100) $[M^+]$, 265 (5) $[M^+-CH_3-CO]$, 238 (13) $[M^+-HNCO-CO]$, 235 (5), 224 (5) 223 (29), 152 (8), 119 (5%). - HRMS calcd. for $C_{18}H_{15}NO_4$ $[M^+]$ 309.1001, found 309.0974. - $C_{18}H_{15}NO_4$ (MW 309.32), Calc.: C 69.89; H 4.89; N 4.53%. Found: C 69.53; H 4.79; N 4.50%.

**3,4-Bis(4-methoxyphenyl)-2,5-dihydrofuran-2,5-dione (8)**

A suspension of imide 7 (0.80 g, 2.6 mmol) in 10% KOH (200 ml) was refluxed for 1 h and then allowed to cool to 25 °C. The solution was filtered and poured into precooled 8 N HCl (200 ml) to give a yellow precipitate. The solid was filtered off, washed with water, and dried to yield anhydride **8** (0.80 g, 75%), mp 170 °C (dec.). - UV ($CH_3OH$): $\lambda_{max}$ (ε) = 206 (16258), 234 (12028), 330 (5679), 396 nm (5906). - IR (KBr) $\tilde{\nu}$ = 3430 (m, br), 3030 (w), 2970 (m), 2940 (m), 2840 (m), 2560 (w), 2040 (w), 1850 (m), 1821 (s), 1752 (s), 1746 (s), 1606 (s), 1575 (m), 1570 (m), 1518 (s), 1505 (s), 1470 (m), 1460 (s), 1450 (m), 1440 (m), 1425 (m), 1422 (m), 1356 (s), 1312 (s), 1297 (s), 1252 (s, br), 1197 (m), 1178 (s), 1130 (m), 1100 (w), 1036 (s), 1026 (s), 975 (w), 952 (w), 935 (m), 928 (s), 860 (w), 840 (s), 812 (m), 790 (m), 742 (m), 635 (w), 615 (m) 580 (s) 532 (s), 515 (m), 440 (w), 410 (w) $cm^{-1}$. - $^1H$ NMR ($CDCl_3$, 300 MHz): δ = 3.84 (s, 6H, 2 x $OCH_3$), 6.56 (d, *J* = 9.0 Hz, 4H), 6.90 (d, *J* = 9.0 Hz, 4H). - $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 55.81 (Ph-$OCH_3$), 114.82 (CH), 120.31 (quart. C), 131.83 (CH), 136.06 (quart. C), 162.08 (C-$OCH_3$), 165.84 (CO). - EI MS (150°C): *m/z* (rel. intensity, %) 311 (17%) [$MH^+$], 310 (100) [$M^+$], 239 (10) [$MH^+$-$CO_2$-CO], 238 (61) [$M^+$-$CO_2$-CO], 223 (32), 195 (7), 152 (8). - $C_{18}H_{14}O_5$ (MW 310.31), Calc. C 69.55, H 4.39%. Found: C 69.67; H 4.55%.

**3,4-Bis(4-hydroxyphenyl)-2,5-dihydrofuran-2,5-dione (9)**

To a solution of **8** (0.80 g, 2.6 mmol) in dry dichloromethane (100 ml) boron tribromide (15.5 ml, 1 M solution in dichloromethane, 15.5 mmol) at -78°C was added dropwise. The yellow colour of the solution immediately turned dark purple. The reaction mixture was allowed to warm to 25 °C, stirred for additional 36 h, and quenched with 2 N NaOH (2 ml). Removal of the organic solvent gave a solid which was suspended in 2 N NaOH (20 ml) and acidified with HCl. The aqueous solution was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give a crude product (0.61 g). Purification was effected by flash column chromatography (chloroform-methanol 10:1) affording 0.56 g of **9** (78%); mp 229-230 °C. - UV ($CH_3OH$): $\lambda_{max}$ (ε) = 208 (19489), 236 (13862), 342 (6888), 406 nm (9715). - IR (KBr): $\tilde{\nu}$ = 3425 (s, br), 1824 (m), 1759 (s), 1742 (s), 1606 (s), 1582 (m), 1510 (m), 1507 (s), 1435 (w), 1351 (s), 1271 (s), 1174 (s), 925 (w), 838 (m), 744 (w), 576 (m), 528 (m) $cm^{-1}$. - $^1H$ NMR ($CDCl_3$, 300 MHz): δ = 6.89 (d, *J* = 8.8 Hz, 4H), 7.46 (d, *J* = 8.8 Hz, 4H), 9.01 (s, br., 2H, OH). - $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ = 116.06 (CH), 119.76 (quart. C), 131.94 (CH), 136.18 (quart. C), 160.00 (C-$OCH_3$), 166.09 (CO). - EI MS (200°C): *m/z* (rel. intensity) 283 (12) [$MH^+$], 282 (70) [$M^+$], 211 (15) [$MH^+$-$CO_2$-CO], 210 (100) [$M^+$-$CO_2$-CO], 181 (8) [$M^+$-$CO_2$-CO-COH], 152 (10) [$M^+$-$CO_2$-CO-2COH], 105 (9%). - $C_{16}H_{10}O_5$ (MW 282.25), Calc. C 68.09; H 3.35%. Found: C 67.97; H 3.71%.

**3,4-Bis-(3,5-dibromo-4-hydroxyphenyl)-2,5-dihydrofuran-2,5-dione (10)**

To a stirred solution of **9** (0.50 g, 1.8 mmol) in glacial acetic acid (50 ml) at 0 °C a solution of bromine (0.36 ml, 7.1 mmol, 6 eq.) in glacial acid (10 ml) was added dropwise. After stirring for 1 h the solution was poured into 10% NaOH (100 ml) to give a red precipitate. The solid was filtered off, washed with cold water, and dried *in vacuo*. Recrystallization from chloroform-hexane yielded **10** as red crystals (0.89 g, 83%); mp 148-149 °C. - UV ($CH_3OH$): $\lambda_{max}$ (ε) = 216 (15523), 280 (8382), 346 (6209), 390 nm (5588). - UV ($CH_3OH$+KOH): $\lambda_{max}$ (ε) = 214 (30894), 278 (9294), 492 nm (1439). - UV ($CH_3OH$+HCl): $\lambda_{max}$ (ε) = 214 (34044), 276 (9950), 332 (6573), 378 nm (5666). - IR (KBr): $\tilde{\nu}$ = 3459 (s,br), 1824 (m), 1761 (s), 1721 (m), 1659 (w), 1787 (m), 1545 (w), 1474 (m), 1450 (w), 1380 (w), 1342 (m), 1321 (m), 1280 (w), 1247 (m), 1190 (m), 1160 (m), 941 (m), 881 (w), 757 (m), 623 (w) $cm^{-1}$. - $^1H$ NMR ([$D_6$]acetone , 300

MHz): δ = 7.80 (s, 4H) - $^{13}$C NMR ($CDCl_3$, 75 MHz): δ = 167.35 (CO), 155.75 (C-OH), 137.98 (quart. C), 136.43 (CH), 124.42 (C-Br), 113.49 (quart. C). - EI MS (240°C): *m/z* (rel. intensity) 602 (17), 211 (15), 600 (61), 598 (94) [$M^+$], 596 (64), 594 (16), 530 (18), 528 (64), 526 (100) [$MH^+$-$CO_2$-CO], 524 (68), 522 (17), 339 (17), 337 (34), 335 (17), 281 (14), 279 (29), 277 (15), 263 (7), 149 (12), 82 (92), 80 (96%).

**Polycitrin A (1a)**

A mixture of **10** (0.50 g, 0.8 mmol), phenol (2 g), diisopropylethylamine (1 ml) and tyramine (0.23 g, 1.6 mmol, 2 eq.) was heated with stirring under argon for 2 h to 140 °C. The dark red melt was cooled, quenched with 2 M HCl (50 ml), and the aqueous solution extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 0.50 g crude product. Purification by flash column chromatography (chloroform-methanol 10:1) yielded **1a** (0.47 g, 78%); mp 180-181°C (Lit.[1] yellowish, fluorescent oil). - UV ($CH_3OH$): $\lambda_{max}$ (ε) = 208 (55365), 276 (13862), 400 nm (4672). - UV ($CH_3OH$/KOH): $\lambda_{max}$ (ε) = 212 (52507), 406 (7075), 512 nm (9470). - IR (KBr): $\tilde{\nu}$ = 3431 (s, br), 1863 (w), 1696 (s), 1625 (w), 1574 (w), 1546 (w), 1515 (m), 1474 (w), 1406 (m), 1350 (w), 1320(m), 1244 (w), 1140 (w), 876 (w), 828 (m), 756 (m), 621 (m) $cm^{-1}$. - $^1$H NMR ($CDCl_3$-[$D_6$]acetone 4:1, 300 MHz): δ = 7.58 (s, 4H), 6.97 (d, *J* = 8.5 Hz, 2 H), 6.69 (d, *J* = 8.5 Hz, 2H), 3.69 (t, *J* = 7.7 Hz, 2H), 2.77 (t, *J* = 7.7 Hz, 2H). - $^{13}$C NMR ($CDCl_3$-[$D_6$]acetone 4:1, 75 MHz): δ = 169.64 (CO), 155.79 (C-OH), 152.08 (C-OH), 133.49 (CH), 132.54 (quart. C), 129.69 (CH), 128.77 (quart. C), 122.39 (quart. C), 115.41 (CH), 110.67 (CBr), 39.94 ($NCH_2$), 33.52 (Ph-$CH_2$). - EI MS (220 °C): *m/z* (rel. intensity) 719 (4), 717 [$M^+$] (6), 715 (4), 601 (6), 600 (4), 599 (20), 598 (5), 597 (30), 595 (18), 552 (9), 528 (10), 526 (12), 524 (9), 369 (10), 368 (25), 337 (9), 313 (11), 264 (11), 256 (8), 239 (9), 236 (16), 185 (7), 129 (13), 125 (12), 123 (11), 120 (100%). - HRMS calcd. for $C_{24}H_{15}Br_4NO_5$ [$M^+$] 716.7647, found 716.7673. - Crystallographic data $C_{24}H_{14}Br_4NO_5 \times \frac{1}{2}\ CHCl_3$, *M* = 776.69, space group *P*-1 (N° 2), triclinic with *a* = 8.091(3), *b* = 11.564(4), *c* = 15.539(3) Å, α = 82.70(3), β = 86.12(2), γ = 84.75(3), *V* = 1341.5(7) Å$^3$, *Z* = 2, $d_c$ = 1.923 g/cm$^3$; Mo-$K_\alpha$ radiation (23 °C); reflections collected 3880, unique reflections 3710, observed reflections 2846 [$I > 2\ \sigma(I)$], R1-index 0.0691 [all data]. The full data for the X-ray crystal structure have been deposited at the Cambridge Crystallographic Data Centre.

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## References and Notes

Dedicated to Professor Dr. Richard Neidlein on the occasion of his 65$^{th}$ birthday.

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