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Concise total synthesis of the aporphine alkaloid 7,7′-bisdehydro-*O*-methylisopiline by an $InCl_3$ mediated cycloisomerization reaction

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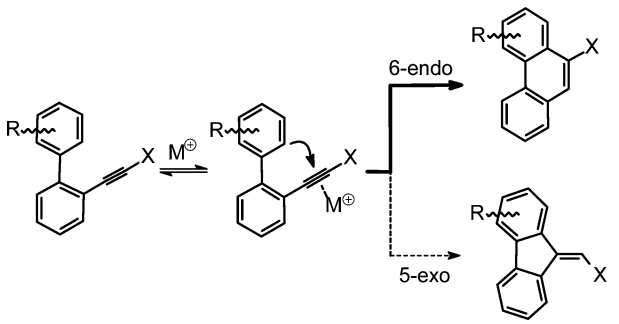
A novel $InCl_3$ mediated cycloisomerization reaction leading to 10-halophenanthrene derivatives constitutes the key step of the first total syntheses of *O*-methyldehydroisopiline 10 and 7,7′-bisdehydro-*O*-methylisopiline 11, two prototype members of the aporphine family of alkaloids.

As part of our ongoing investigations on metal catalyzed skeletal rearrangements[1] we have recently developed a new entry into highly substituted phenanthrenes and related polycyclic arenes based on the cycloisomerization process depicted in Scheme 1 (X = H, alkyl).[2] $PtCl_2$ turned out to be the catalyst of choice, triggering the desired 6-*endo* cyclizations with high selectivity in all but one case.[3]

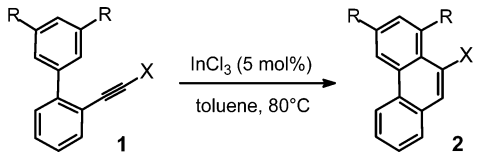


Scheme 1 Metal catalyzed cycloisomerization of *ortho*-alkynylated biphenyl derivatives.

Therefore we were surprised to find that the corresponding haloalkyne derivatives (X = Cl, Br) react rather poorly under these conditions. In addition to the expected 10-halophenanthrenes, significant amounts of the corresponding alkenylidene fluorenes are formed *via* the competing 5-*exo*-cyclization pathway. In an attempt to improve on this result, a set of different metal species was screened for catalytic activity. Among them, $InCl_3$ turned out to be optimal, effecting the desired transformation with good to excellent yields and high selectivity (Table 1).[4]

The resulting 10-halophenanthrenes are ideally suited for further elaboration. This is exemplified by the first total synthesis of *O*-methyldehydroisopiline **10** isolated from the leaves of the annonaceous plant *Gutteria ouregon*,[5] and its symmetrical dimer **11**, a secondary metabolite of the tropical trees *Polyalthia bullata*[6] and *Phoenicanthus obliqua*.[7] These compounds are prototype members of the aporphine family, a large and rapidly growing class of isoquinoline alkaloids endowed with an impressive number of biological activities.[8]

Table 1 $InCl_3$ catalyzed synthesis of 10-halophenanthrenes

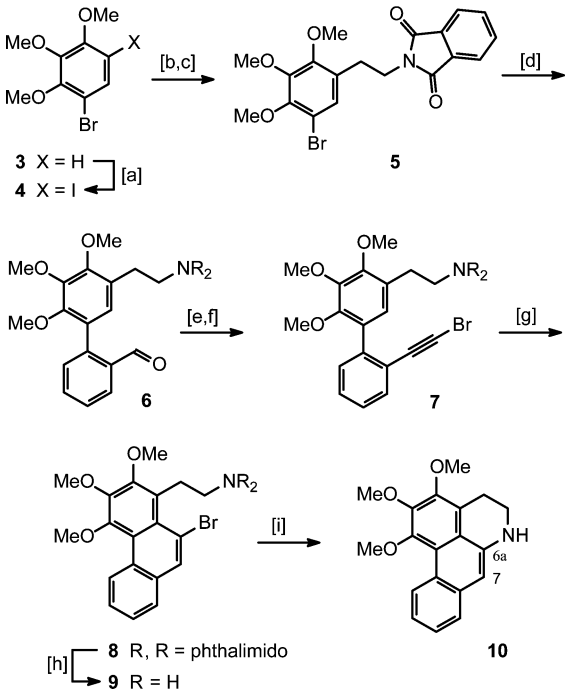


1 **2**

Entry	R	X	Yield (%)[a]
1	Me	Cl	90
2	Me	Br	77
3	OMe	Cl	90
4	OMe	Br	59[b]

[a] Isolated yield unless stated otherwise. [b] GC yield.

Selective iodination of commercial bromotrimethoxybenzene **3** furnishes compound **4**[9] which undergoes a selective activation of its C–I bond in the presence of a catalyst formed *in situ* from $Pd(OAc)_2$ and tri-*o*-tolylphosphine. The resulting organopalladium species reacts with commercial *N*-vinylphthalimide in a standard Heck reaction[10] to afford the corresponding enamide[11] which is chemoselectively hydrogenated in the presence of Crabtree's catalyst[12] without damaging the residual bromide function. The resulting compound **5** allows for a subsequent Suzuki coupling[13] with commercial 2-formylbenzeneboronic acid to give the highly functionalised biphenyl derivative **6** in 94% yield. Conversion of its aldehyde group into the desired bromoalkyne **7** follows standard procedures[14] and sets the stage for the envisaged carbocyclization to form the phenanthrene core. Gratifyingly, this key transformation worked exquisitely well in the presence of $InCl_3$ in toluene at 80 °C. The phthalimide protecting group in phenanthrene **8** thus formed was cleaved off by hydrazinol-



Scheme 2 *Reagents and conditions*: [a] I_2, HgO, CH_2Cl_2, r.t., 81%; [b] $Pd(OAc)_2$ cat., P(o-tol)$_3$ cat., *N*-vinylphthalimide, iPrNEt$_2$, MeCN, 100 °C, 57%; [c] [Ir(COD)Py(PCy$_3$)]PF_6 cat., H_2 (1 atm), CH_2Cl_2, quant.; [d] 2-formylbenzeneboronic acid, $Pd(OAc)_2$ cat., Cy_2P(*o*-biphenyl) cat., K_3PO_4, toluene, 94%; [e] CBr_4, PPh_3, CH_2Cl_2, 0 °C, 88%; [f] DBU, DMSO, 15 °C, 79%; [g] $InCl_3$ (1 eq.), toluene, 80 °C, 87%; [h] hydrazine, MeOH, reflux, quant.; [i] CuI, CsOAc, DMSO, 71%.

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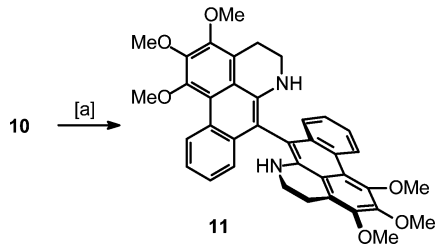

Scheme 3 *Reagents and conditions*: [a] $CuCl_2{\cdot}2H_2O$, $tBuNH_2$, MeOH, 86%.

ysis to give compound **9** which is set up for a smooth intramolecular amination reaction in the presence of CuI and CsOAc as the promoters forging the heterocyclic ring.[15] This high yielding step completes the first total synthesis of O-methyl-dehydroisopiline **10** (Scheme 2). The spectroscopic data† of this prototype 6a,7-dehydroaporphine derivative[16] are in full accord with the proposed structure.[17]

Since 6a,7-dehydroaporphines in general are known to behave like enamines,[18] it was anticipated that a selective activation of the 7-position in **10** might be possible, thus allowing direct conversion of this compound to the corresponding symmetrical dimer **11** (Scheme 3). While the use of $PhI(OAc)_2$, $Hg(OAc)_2$, I_2, or air, which were previously recommended for such purposes,[19] was unsuccessful in our hands leading either to no conversion or to a rapid degradation of the starting material, we were pleased to find that a combination of $CuCl_2{\cdot}2H_2O$ and $tBuNH_2$ in MeOH effected the desired oxidative coupling in satisfactory yields.[20] The spectral data† of the resulting 7,7′-bisaporphine derivative **11** are in excellent agreement with those reported in the literature.[6,17]

In summary, a straightforward entry into the dehydroaporphine series is described based on a highly productive sequence of metal-catalyzed and -mediated transformations relying on In(3+), Pd(0), Ir(1+), Cu(1+) and Cu(2+) as the active components. Due to the flexibility inherent to this route and the fact that dehydroaporphines can be further elaborated into a host of other (natural) products, this approach provides ample opportunity for further exploration of this important class of bioactive natural products.

Notes and references

† Data of compound **10**: IR (KAP) 3374, 2933, 2832, 1623, 1391, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.24 (t, J = 6.1 Hz, 2H), 3.47 (t, J = 6.0 Hz, 2H), 3.98 (s, 6H), 4.06 (s, 3H), 6.79 (s, 1H), 7.35 (dt, J = 8.5, 1.6 Hz, 1H), 7.44 (dt, J = 7.8, 1.1 Hz, 1H), 7.58 (dd, J = 8, 1.5 Hz, 1H), 9.40 (d, J = 8.6, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 40.7, 60.2, 60.9, 61.3, 105.1, 120.4, 121.2, 123.0, 125.1, 125.8, 126.3, 127.1, 133.6, 140.6, 146.4, 148.4, 151.1. MS (EI) m/z (rel. intensity): 309 ([M^+], 100), 294 (26), 266 (11). Data of compound **11**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.14–3.34 (m, 8H), 4.00 (s, 6H), 4.06 (s, 6H), 4.14 (s, 6H), 7.15 (dd, J = 8.2, 1.3 Hz, 2H), 7.22 (ddd, J = 8.4, 6.4, 1.2 Hz, 2H), 7.35 (ddd, J = 8.8, 6.4, 1.6, 2H), 9.57 (dd, J = 8.6, 0.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 40.6, 60.4, 60.9, 61.3, 120.2, 121.9, 123.1, 123.9, 125.5, 126.8, 127.3, 132.7, 139.6, 146.7, 148.6, 151.1. MS (EI) m/z (rel. intensity): 616 ([M^+], 100), 308 (12), 294 (12).

1 (*a*) A. Fürstner, H. Szillat, B. Gabor and R. Mynott, *J. Am. Chem. Soc.*, 1998, **120**, 8305; (*b*) A. Fürstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785; (*c*) A. Fürstner, F. Stelzer and H. Szillat, *J. Am. Chem. Soc.*, 2001, **123**, 11863.

2 A. Fürstner and V. Mamane, *J. Org. Chem.*, 2002, **67**, 6264.

3 Reviews on the use of $PtCl_2$ in organic synthesis: (*a*) M. Méndez and A. M. Echavarren, *Eur. J. Org. Chem.*, 2002, **15**; (*b*) G. C. Lloyd-Jones, *Org. Biomol. Chem.*, 2003, **1**, 215; (*c*) C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; (*d*) M. Méndez, V. Mamane and A. Fürstner, *Chemtracts – Org. Chem.*, 2003, **16**, 397; (*e*) for a pioneering study see: N. Chatani, N. Fukukawa, H. Sakurai and S. Murai, *Organometallics*, 1996, **15**, 901.

4 Reviews on $InCl_3$ in synthesis: (*a*) P. Cintas, *Synlett*, 1995, 1087; (*b*) K. K. Chauhan and C. G. Frost, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3015; (*c*) B. C. Ranu, *Eur. J. Org. Chem.*, 2000, 2347.

5 D. Cortes, R. Hocquemiller, M. Leboeuf, A. Cavé and C. Moretti, *J. Nat. Prod.*, 1986, **49**, 878.

6 J. D. Connolly, M. E. Haque and A. A. Kadir, *Phytochemistry*, 1996, **43**, 295.

7 (*a*) E. M. K. Wijeratne, B. D. Lankananda, Y. Tezuka, T. Nagaoka and A. A. L. Gunatilaka, *J. Nat. Prod.*, 2001, **64**, 1465; (*b*) for closely related dimers see: S. Kanokmedhakul, K. Kanokmedhakul, D. Yodbuddee and N. Phonkerd, *J. Nat. Prod.*, 2003, **66**, 616.

8 H. Guinaudeau, M. Lebouef and A. Cavé, *J. Nat. Prod.*, 1988, **51**, 389 and references cited therein.

9 K. Orito, T. Hatakeyama, M. Takeo and H. Suginome, *Synthesis*, 1995, 1273.

10 (*a*) I. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009; (*b*) A. de Meijere and F. E. Meyer, *Angew. Chem.*, 1994, **106**, 2473; A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379.

11 Some α-arylation product is also formed which is easily removed by flash chromatography.

12 R. H. Crabtree, H. Felkin, T. Fellebeen-Khan and G. E. Morris, *J. Organomet. Chem.*, 1979, **168**, 183.

13 (*a*) J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550; (*b*) review: A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147.

14 (*a*) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769; (*b*) V. Ratovelomana, Y. Rollin, C. Gébéhenne, C. Gosmini and J. Périchon, *Tetrahedron Lett.*, 1994, 4777.

15 K. Yamada, T. Kubo, H. Tokuyama and T. Fukuyama, *Synlett*, 2002, 231.

16 See the following for leading references on previous syntheses of 6a,7-dehydroaporphines and references cited therein: (*a*) M. P. Cava, I. Noguchi and K. T. Buck, *J. Org. Chem.*, 1973, **38**, 2394; (*b*) G. R. Lenz and F. J. Koszyk, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1273; (*c*) C. Saá, E. Guitian, L. Castedo and J. M. Saá, *Tetrahedron Lett.*, 1985, **26**, 4559; (*d*) M. P. Cava, D. L. Edie and J. M. Saá, *J. Org. Chem.*, 1975, **40**, 3601; (*e*) N. C. Yang, G. R. Lenz and A. Shani, *Tetrahedron Lett.*, 1966, 2941; (*f*) K. Orito, S. Uchiito, Y. Satoh, T. Tatsuzawa, R. Harada and M. Tokuda, *Org. Lett.*, 2000, **2**, 307.

17 Note that *O*-methyldehydroisopiline **10** isolated from the natural source had not been obtained in analytically pure form. Its spectral data, however, allowed for an unambiguous determination of its structure, *cf.* ref. 5. In contrast, the synthetic material gave fully satisfactory data. It is important to mention, however, that **10** is unstable when exposed to air, as can be judged from a rather rapid coloration of the sample. Likewise, compound **11** is unstable in solution as can be seen from a characteristic color change from yellow to green.

18 A. Venkateswarlu and M. P. Cava, *Tetrahedron*, 1976, **32**, 2079.

19 (*a*) S. Ruchirawat and S. Predapitakkun, *Heterocycles*, 2001, **55**, 371; (*b*) M. Gerecke, R. Borer and A. Brossi, *Helv. Chim. Acta*, 1975, **58**, 185; (*c*) L. Castedo, R. Riguera, J. M. Saá and R. Suau, *Heterocycles*, 1977, **6**, 677.

20 M. Smrčina, Š. Vyskočil, B. Máca, M. Polášek, T. A. Claxton, A. P. Abbott and P. Kočovský, *J. Org. Chem.*, 1994, **59**, 2156.