Pergamon

Tetrahedron Letters 43 (2002) 4609–4612

TETRAHEDRON LETTERS

Aglairubine—discrepancies during the course of structure elucidation

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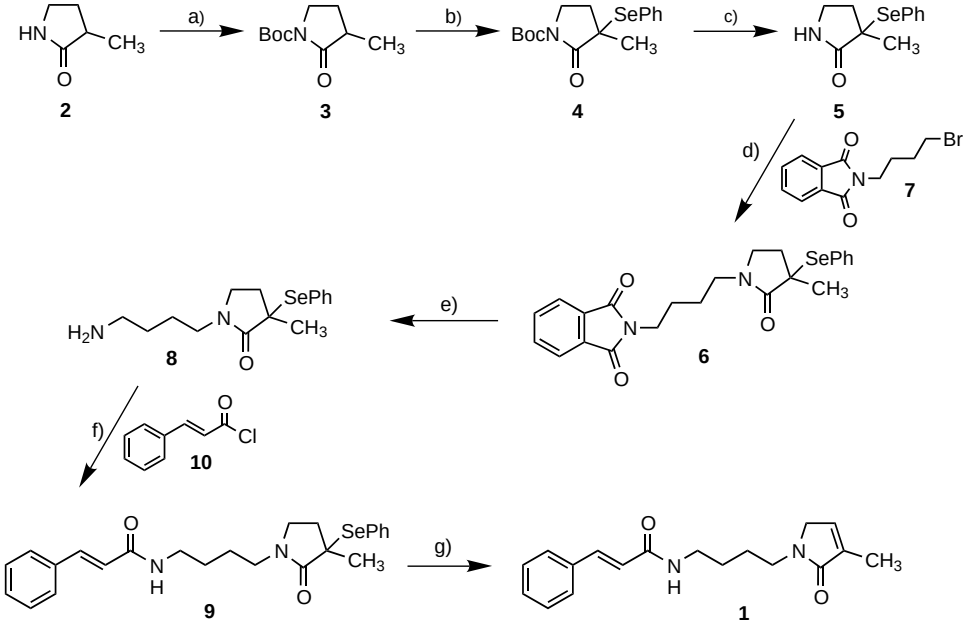
Received 2 May 2002; accepted 7 May 2002

Abstract—A short synthesis of the originally proposed structure **1** for the putrescine alkaloid aglairubine is presented as well as for a conceivable structure alternative **11**. Due to the ascertained mismatch of spectroscopical data for synthetic and natural compounds, the published aglairubine structure has to be revised.

A short communication, published by Saifah and Suparakchinda in 1998,[1] dealt with isolation and structure elucidation of a formerly unknown putrescine alkaloid, named aglairubine. This alkaloid was isolated from the leaves of *Aglaia rubigenosa* (Hiern) Pannel, a plant that belongs to the genus Meliaceae. *Aglaia* species—especially widespread in the southeastern part of Asia—are well known as a rich source of putrescine alkaloids, a subclass of the common, but rather unsystematically distributed class of polyamine alkaloids. The published aglairubine structure attracted our attention due to the fact that one of the amide moieties is incorporated in an unsaturated five-membered ring. Contrary to this, all other putrescine bisamides known



Scheme 1. (a) Boc_2O, NEt_3, DMAP, CH_3CN, rt, 10 h, quant. (b) KHMDS, PhSeBr, Et_2O, −65°C, 30 min, 89%. (c) CF_3COOH, toluene, rt, 1 h, 83%. (d) KHMDS, **7**, DMF, 0°C→rt, 10 h, 60%. (e) NH_2-NH_2, EtOH, reflux, 2 h, 90%. (f) NEt_3, **10**, CH_2Cl_2, rt, 15 min, 95%. (g) MCPBA, CH_2Cl_2, −35°C→rt, 2 h, 94%.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)00869-9

so far as natural occurring alkaloids[2] show an open chain structure i.e. the amide groups are not incorporated in a cyclic framework.[3] In the course of our study of such compounds, we decided to synthesise this alkaloid in order to compare the spectroscopical data and to verify this new structure type.

For this purpose, we were watching out for a synthesis sequence which could bring up the desired structure unequivocally, so the synthesis itself had to be an independent source of information of the final structure to accompany the structure elucidation by spectroscopic means.

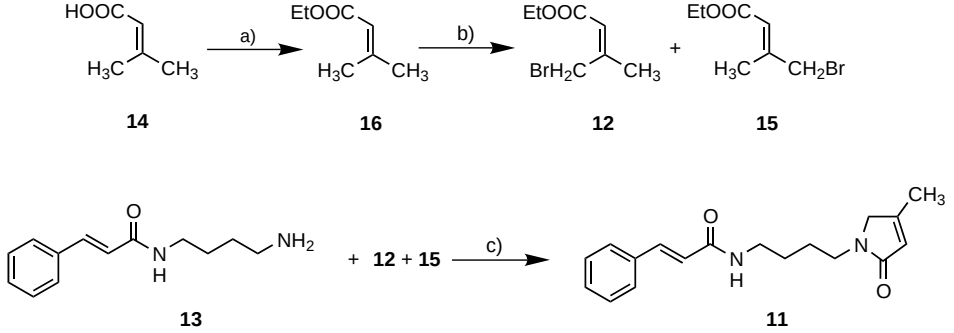
As a starting material for the synthesis shown in Scheme 1 served commercially available 3-methyl-2-pyrrolidone (**2**). Boc-protection of this cyclic amide to *tert*-butyl 3-methyl-2-oxo-1-pyrrolidine-carboxylate (**3**) could be performed in excellent yield using a protocol of Grehn et al.,[4] which describes the reaction of Boc_2O with amides in acetonitrile in the presence of catalytic amounts of DMAP. The double bond needed in the target structure **1** could be introduced in a latent form, using the versatile phenylselenyl group, so deprotonation of **3** by KHMDS at low temperature and subsequent addition of phenylselenyl bromide resulted quickly in **4**.[5] For the following Boc-deprotection, we found it much more convenient, in view of reaction time, to use TFA in toluene instead of the more commonly used halogenated solvents. The free amide **5**[6] obtained could be successfully alkylated to **6**[7] by *N*-(4-bromobutyl)phthalimide (**7**), using DMF as solvent and KHMDS again as a base. The putrescine core thus constructed in **6** now demanded the liberation of the amine functionality to bring in the cinnamic acid residue in the next step. Hydrazinolysis of the phthalimide group in EtOH worked well and allowed isolation of free amine **8**[8] without problems. With **8** in hand, it was easy to isolate **9**[9] after acylation with cinnamoyl chloride (**10**). Compound **9** represented the whole skeleton of structure **1**, besides the double bond. We were pleased to see that a simple oxidation of the phenylselenyl group by MCPBA as an oxidant at lower temperatures resulted in the desired **1**[10] by means of the scheduled elimination reaction.

The reaction sequence presented allowed the isolation of **1** in a few hundred-milligram scale, enabling spectral measurements comfortably. Surprisingly for such a rather uncomplicated structure without any stereogenic centre, the NMR data published did *not* fit with our measured spectra. Of course, care has been taken to use the same conditions of measurement as in literature. In order to be completely sure about the structure of our product, we examined it extensively by two-dimensional NMR spectroscopy (HSQC, COSY, HMBC and even INADEQUATE). Not surprisingly, all of our recorded data perfectly confirmed the structure of **1**.

Due to the significant differences with the published data by Saifah and Suparakchinda for aglairubine, we have therefore to conclude that either their structure elucidation is wrong or there are some problems in the analytical data set published. The published NMR spectra for aglairubine are definitely not in accordance with structure **1**.

Unfortunately, we could not examine the natural product ourselves because of a lack of material. On the other hand, we took into consideration that only the position of the methyl group on the five-membered ring might be wrong in structure **1**. We assumed that a methyl group shifted to the neighbouring position—as shown in structure **11**—could possibly be the correct structure for natural aglairubine. To survey this presumption, we decided also to synthesise structure **11**, using the pathway presented in Scheme 2. The reaction of ethyl (*Z*)-4-bromo-3-methyl-2-butenoate (**12**) with easily obtainable mono-cinnamoyl-putrescine (**13**)[11] allowed isolation of the desired **11** in one single step, so a highly effective synthesis was at hand. Bromo ester **12** itself could be obtained from commercially available 3-methyl-but-2-enoic acid (**14**), following a method described by Mata and Thomas.[12] It may be added that a possible, but somewhat tedious chromatographic separation of both geometric isomers **12** and **15**, obtained in a ratio of nearly 1:1 by the NBS bromination of ethyl 3-methyl-2-butenoate (**16**), proved to be dispensable for a successful synthesis of **11**.[13] For obvious reasons of hindered rotation around the double bond, only the (*Z*)-isomer **12** can undergo the cyclisation to the five-membered ring in **11**.

Again, we used the same extensive NMR spectroscopical examination as mentioned above to successfully authenticate our synthetic product. Disappointingly,



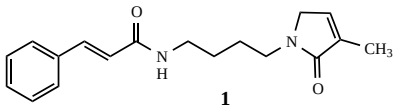
Scheme 2. (a) EtOH, H_2SO_4, reflux, 10 h, 72%. (b) NBS, AIBN, CCl_4, reflux, 3 h, 96%. (c) NEt_3, CH_2Cl_2, reflux, 1.5 h, 30%.[14]

the new structure **11** also did not fit the published spectroscopical data and had therefore to be excluded as a structure alternative for aglairubine, provided that the published NMR spectra are correct for isolated aglairubine.

Conclusion

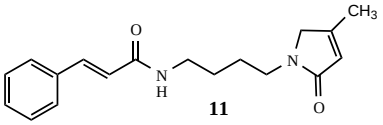
Neither the originally proposed structure **1** nor the structural alternative **11** show identity in NMR-spectroscopical data with the published spectra by Saifah and Suparakchinda.[1] If there was no mistake during their publication procedure for these data, the structure **1** is in fact incorrect. At least, the already published NMR spectra are definitely wrong for compound **1**. The correct spectra for **1** and **11** are presented in our Tables 1 and 2. A final decision about the virtual aglairubine structure demands for a new structure elucidation on authentically material.

Table 1. Comparison of the ^{1}H NMR data (CD_3OD, 500 MHz) of the synthesised compounds **1** and **11** with the published spectra for aglairubine



1

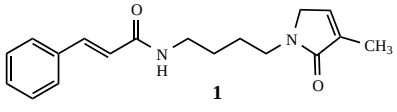
Published ^{1}H NMR for aglairubine[1]



11

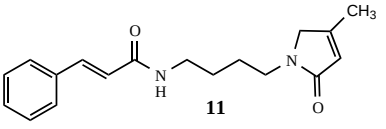
$\Delta\delta$ in ppm	[ppm]	[ppm]	[ppm]	$\Delta\delta$ in ppm
+0.11	7.65 (2H)	7.54 (2H)	7.56 (2H)	**+0.02**
+0.08	7.60 (1H)	7.52 (1H)	7.52 (1H)	**0.0**
+0.07	7.45 (3H)	7.38 (2H)	7.36 (3H)	**−0.02**
		7.36 (1H)		**0.0**
+0.09	6.68 (1H)	6.59 (1H)	6.59 (1H)	**0.0**
+0.61	6.94 (1H)	6.33 (1H)	5.79 (1H)	**−0.54**
−0.28	3.95 (2H)	4.23 (2H)	4.02 (2H)	**−0.21**
+0.26	3.58 (2H)	3.32 (2H)	3.45 (2H)	**+0.13**
+0.14	3.42 (2H)	3.28 (2H)	3.34 (2H)	**−0.06**
+0.10	1.93 (3H)	1.83 (3H)	2.08 (3H)	**+0.25**
+0.12	1.72 (2H)	1.60 (4H)	1.65 (2H)	**+0.05**
+0.04	1.64 (2H)		1.56 (2H)	**−0.04**

Table 2. Comparison of the ^{13}C NMR data (CD_3OD, 500 MHz) of the synthesised compounds **1** and **11** with the published spectra for aglairubine



1

Published ^{13}C NMR for aglairubine[1]



11

$\Delta\delta$ in ppm	[ppm]	[ppm]	[ppm]	$\Delta\delta$ in ppm
+2.4	174.4	172.0	174.8	**+2.8**
+0.2	168.8	168.6	168.8	**+0.2**
+1.0	141.8	140.8	141.8	**+1.0**
+0.3	136.5	136.2	136.5	**+0.3**
+2.5	138.4	135.9	122.7	**−13.2**
+3.5	136.0	132.5	159.4	**+26.9**
+0.2	130.9	130.7	130.9	**+0.2**
0.0	130.1	130.1 (2C)	130.1	**0.0**
−0.5	128.9	129.4 (2C)	128.9	**−0.5**
+0.3	122.1	121.8	122.1	**+0.3**
−7.2	52.3	59.5	57.2	**−2.3**
+3.0	43.3	40.3	42.8	**+2.5**
+0.1	40.3	40.2	40.3	**+0.8**
+0.1	27.9	27.8 (2C)	27.8	**+0.0**
−0.6	27.2		27.2	**−0.6**
−1.6	11.4	13.0	15.2	**+2.2**

Acknowledgements

We thank the NMR department of our institute and especially Mrs. Nadja Walch for recording the INADEQUATE spectra. Furthermore, the Swiss National Science Foundation is gratefully acknowledged for generous support.

References

1. Saifah, E.; Suparakchinda, N. *Planta Med.* **1998**, *64*, 682.
2. For a review about polyamine chemistry as well as a complete list of all up to June 2000 published polyamine alkaloids see: Bienz, S.; Detterbeck, R.; Ensch, C.; Guggisberg, A.; Häusermann, U.; Meisterhans, C.; Wendt, B.; Werner, C.; Hesse, M. In *Putrescine*, *Spermine*, *Spermidine*, *and Related Polyamine Alkaloids*; Cordell, G. A., Ed; Academic Press: New York, 2002; in press.
3. There is indeed a whole class of cyclic polyamine alkaloids existing, which are derived from putrescine, but they all possess the special 2-aminopyrrolidine skeleton and are therefore considered as their own subclass.
4. Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand. B* **1986**, *40*, 745–750.
5. *tert*-Butyl 3-methyl-2-oxo-3-(phenylselanyl)-1-pyrrolidinecarboxylate (**4**): Oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, $J=8.0$ Hz, 2H), 7.41–7.38 (m, 1H), 7.33–7.27 (m, 2H), 3.59–3.55 (m, 1H), 3.38–3.34 (m, 1H), 2.30–2.20 (m, 1H), 2.12–2.00 (m, 1H), 1.59 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (s), 150.2 (s), 137.7 (d), 129.5 (d), 128.8 (d), 126.2 (s), 82.6 (s), 49.6 (s), 42.9 (t), 33.5 (t), 27.9 (q), 24.1 (q).
6. 3-Methyl-3-(phenylselanyl)-2-pyrrolidinone (**5**): IR ($CHCl_3$): ν 3439, 3021, 1697, 1622, 1476, 1417, 1376, 1305, 1273, 1213, 1102, 661, 561 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, $J=6.8$ Hz, 2H), 7.42–7.32 (m, 1H), 7.31–7.27 (m, 2H), 6.90 (br, 1H), 3.17–3.11 (m, 1H), 3.07–2.99 (m, 1H), 2.41–2.33 (ddd, 1H), 2.23–2.12 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9 (s), 137.6 (d), 129.1 (d), 128.8 (d), 126.8 (s), 48.3 (s), 39.1 (t), 37.1 (t), 24.3 (q); CIMS (NH_3): m/z 273 (100, $[M+18]^+$), 256 (54, $[M+1]^+$).
7. 2-{4-[3-Methyl-2-oxo-3-(phenylselanyl)-1-pyrrolidinyl]-butyl}1*H*-isoindole-1,3(2*H*)-dione (**6**): Oil; IR ($CHCl_3$): ν 3040, 2990, 2940, 2860, 1770, 1710, 1680, 1615, 1470, 1435, 1395, 1370, 1360, 1330, 1280, 1265, 1100, 1040, 1020, 1000, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.80 (m, 2H), 7.74–7.66 (m, 2H), 7.65–7.63 (m, 2H), 7.38–7.25 (m, 3H), 3.69 (t, $J=7.0$ Hz, 2H), 3.33–3.23 (m, 1H), 3.18–3.03 (m, 2H), 2.97–2.89 (m, 1H), 2.37–2.29 (ddd, 1H), 2.13–2.03 (m, 1H), 1.72–1.60 (m, 2H), 1.58 (s, 3H), 1.57–1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (s), 168.2 (s), 137.7 (d), 133.8 (d), 132.0 (s), 129.0 (d), 128.6 (d), 126.8 (s), 123.1 (d), 49.4 (s), 43.9 (t), 42.4 (t), 37.4 (t), 35.1 (t), 25.9 (t), 24.7 (q), 24.4 (t); CIMS (NH_3): m/z 457 (100, $[M+1]^+$), 299 (56, $[M-C_6H_5Se]^+$).
8. 1-(4-Aminobutyl)-3-methyl-3-(phenylselanyl)-2-pyrrolidinone (**8**): Oil; IR ($CHCl_3$): ν 2990, 2930, 2860, 1675, 1475, 1450, 1435, 1370, 1280, 1100, 1020, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, $J=8.0$ Hz, 2H), 7.41–7.26 (m, 3H), 3.27–2.94 (m, 4H), 2.72 (t, $J=6.7$ Hz, 2H), 2.37–2.30 (ddd, 1H), 2.13–1.96 (m, 1H), 1.80 (br, 2H), 1.59 (s, 3H), 1.58–1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (s), 137.7 (d), 129.0 (d), 128.6 (d), 126.8 (s), 49.5 (s), 43.9 (t), 42.7 (t), 41.5 (t), 35.1 (t), 30.4 (t), 24.8 (t), 24.4 (q); CIMS (NH_3): m/z 327 (100, $[M+1]^+$), 169 (8, $[M-C_6H_5Se]^+$).
9. (*E*)-*N*-{4-[3-Methyl-2-oxo-3-(phenylselanyl)-1-pyrrolidinyl]butyl}-3-phenyl-2-propenamide (**9**): Oil IR ($CHCl_3$): ν 3470, 3300, 3060, 2990, 2920, 2860, 1665, 1625, 1575, 1510, 1450, 1435, 1370, 1330, 1280,1105, 985, 975, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.59 (m, 3H), 7.51–7.46 (m, 2H), 7.39–7.25 (m, 6H), 6.72 (t, $J=5.3$ Hz, 1H), 6.50 (d, $J=15.7$ Hz, 1H), 3.43–3.37 (m, 2H), 3.29–2.94 (m, 4H), 2.37–2.30 (m, 1H), 2.16–2.02 (m, 1H), 1.60 (s, 3H), 1.62–1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4 (s), 166.1 (s), 140.3 (d), 137.7 (d), 135.0 (s), 129.3 (d), 129.2 (d), 128.7 (d), 128.6 (d), 127.7 (d), 126.7 (s), 121.1 (d), 49.5 (s), 44.0 (t), 42.5 (t), 39.3 (t), 35.0 (t), 26.0 (t), 24.8 (t), 24.8 (q); CI-MS (NH_3): m/z 457 ($[M+1]^+$).
10. (*E*)-*N*-[4-(3-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-butyl]-3-phenyl-2-propenamide (**1**): Oil IR ($CHCl_3$): ν 3450, 3300, 3300, 2970, 2860, 1670, 1645, 1630, 1580, 1515, 1460, 1450, 1415, 1335, 1240, 990, 980, 910, 815 cm^{-1}; CI-MS (NH_3): m/z 299 ($[M+1]^+$). For the NMR data of structure **1** see Tables 1 and 2.
11. Experimental details for the synthesis of *N*-mono-cinnamoyl-putrescine (**13**) are published elsewhere: Detterbeck, R.; Hesse, M.; *Tetrahedron* **2002**, in press.
12. Mata, E. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 785–799.
13. (*E*)-*N*-[4-(4-Methyl-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-butyl]-3-phenyl-2-propenamide (**11**): Oil IR ($CHCl_3$): ν 3440, 3300, 2995, 2930, 2860, 1670, 1630, 1580, 1550, 1510, 1460, 1450, 1410, 1330, 1150, 985, 975, 940, 840 cm^{-1}; CIMS (NH_3): m/z 299 ($[M+1]^+$); EI MS: m/z 298 (71, $[M]^{+\bullet}$), 152 (51, $[M-C_6H_5CHCHCONH]^+$), 131 (100, $[M-C_6H_5CHCHCO]^+$), 103 (63, $[C_6H_5CHCH]^+$), 77 (32, $[C_6H_5]^+$). The NMR spectra of structure **11** are given in Tables 1 and 2.
14. No efforts have been undertaken to optimise the reaction conditions.