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The homologous *tert*-amino effect: a route to fused 2-benzazepine derivatives

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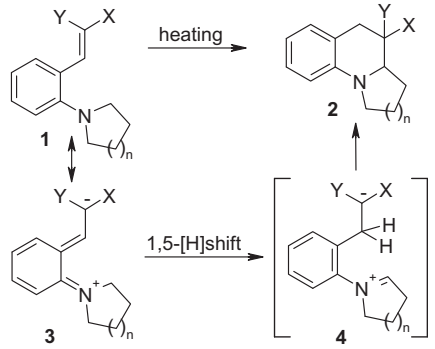
ABSTRACT

2-Cyano- and 2-carbethoxy-3-[2-(pyrrolidin-1-ylmethyl)phenyl]acrylonitriles were prepared through either amination of appropriate 3-[2-(bromomethyl)phenyl]acrylonitriles with pyrrolidine or condensation of 2-(pyrrolidin-1-ylmethyl)benzaldehyde with malononitrile and ethyl cyanoacetate. These acrylonitrile derivatives were shown to undergo easy mutual interconversion with 1-(pyrrolidin-1-yl)indane-2-carbonitriles driven by solvent polarity. Upon heating at 140–150 °C both acrylonitrile and indane derivatives were found to give 2,3,5,10,11,11*a*-hexahydro-1*H*-pyrrolo[1,2-*b*][2]benzazepine-11-carbonitriles. All transformations observed were rationalized in the terms of reactions related to the *tert*-amino effect. Furthermore, the corresponding piperidin-1-yl and azepan-1-yl analogs of the above acrylonitriles and indanes were obtained similarly. By analogy their heating afforded 1,2,3,4,6,11,12,12*a*-octahydropyrido[1,2-*b*][2]benzazepine-12-carbonitriles and 7,8,9,10,11,11*a*, 12,13-octahydro-5*H*-azepino[1,2-*b*][2]benzazepine-12-carbonitriles.

1. Introduction

In the eighties Verboom and Reinhoudt developed an efficient method[1–6] for the preparation of fused tetrahydroquinolines using the so-called *tert*-amino effect (Scheme 1). The term was specially coined[7,8] to describe this type and related cyclizations. Thus upon heating the Knoevenagel adducts **1** in high-boiling polar solvents the quinoline derivatives **2** were isolated in good yields.[1–6]



Scheme 1. The typical *tert*-amino effect cyclization. n=1, 2. X and Y are the electron-withdrawing groups like CN, COOR etc.

The stereochemical and kinetic aspects of the *tert*-amino effect were thoroughly investigated[3–6] and the mechanism was suggested. Thus, the reaction was assumed to proceed through a suprafacial sigmatropic hydrogen 1,5-shift occurring from the canonic structure **3** and further ring closure of the bipolar intermediate **4**.[3–6] Later this cyclization was extensively studied varying the *tert*-amine framework,[9–12] the methylene component,[13–15] and replacing the benzene moiety with heteroaromatics.[16–19] These efforts are summarized in the recent reviews.[20,21] Moreover, recently *tert*-amino effect type reactions were reported for biphenyl,[22] 1,2-bis(aryl)arene,[23] and *peri*-naphthalene[24] systems. In the course of our research[12,16] on the *tert*-amino effect we have taken an interest in the compounds of type **8**,**9** (Scheme 2), the homologs of derivatives **1** with benzene and tertiary amine moieties separated by methylene group. Are the *tert*-amino effect reactions possible for this system? Since nothing was previously known we have studied the question and report the results herein.

2. Results and discussion

There are two possible approaches to the target compounds **8**,**9**. The first one (route **A**) includes amination of derivatives **5**,**6** available through a bromination of the appropriate 2-methylcinnamonitriles.[25] The second one (route **B**) is based on the condensation of aldehydes **7a**–**c** with malononitrile or ethyl cyanoacetate. The starting aldehydes **7** were prepared as reported.[26,27] The both

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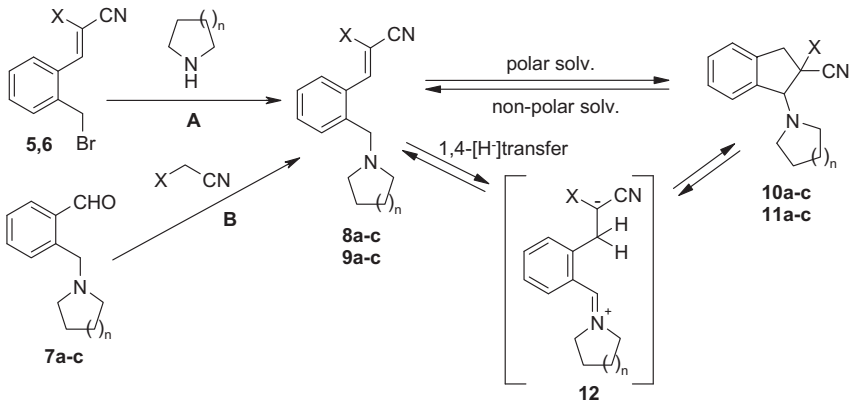
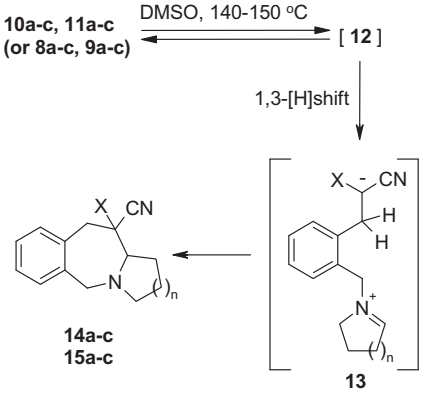


Scheme 2. *X*=**5**, **8**, **10**: CN; **6**, **9**, **11**: COOEt. *n*=**a**: 1; **b**: 2; **c**: 3.

approaches were employed yielding the same compounds identified as indanes **10a**–**c**, **11a**–**c** on the basis of their ^{1}H and ^{13}C NMR spectra recorded in DMSO-d_6 or acetone-d_6 solutions. Surprisingly, when the spectra of these compounds were recorded in $CDCl_3$ or C_6D_6 solutions they exhibited sets of signals corresponding to the Knoevenagel adducts structures **8a**–**c**, **9a**–**c**. So, the materials obtained undergo easy mutual interconversion between cinnamonitrile **8**,**9** and indane **10**,**11** structures driven by the solvent polarity. Nevertheless derivatives **8**,**9** and **10**,**11** are rather the different substances separated by a low energy barrier, than an equilibrium mixture. Thus, we failed to record an equilibrium spectrum for the compound **8a** (**10a**) in the mixtures of $CDCl_3$ and DMSO-d_6. Instead, when the concentration of DMSO-d_6 in $CDCl_3$ solution increased up to 20% (by volume) complete and instantaneous transformation of cinnamonitrile **8a** into indane **10a** was observed.

We suppose the conversion of cinnamonitriles **8**,**9** into indanes **10**,**11** is the result of reversible *tert*-amino effect type reaction occurring through the bipolar intermediate **12**. The latter is formed from the derivatives **8**,**9** by means of 1,4-hydride transfer. It should be noted that preparation of close related indanes from the compounds like **5**,**6** through the tandem process including Michael addition to the double bond followed by intramolecular alkylation was reported previously.[25,28–31] However, formation of the same derivatives **8**–**11** via the route **B** provides clear evidence of the *tert*-amino effect (for other approaches to related indanes see [32–37]).

Since typically the *tert*-amino effect (Scheme 1) is observed at elevated temperatures,[1–19] the thermal behavior of the prepared compounds **8**–**11** was studied. It was found that heating derivatives **10a**,**11a** (or **8a**,**9a**) in DMSO at 140–150 °C afforded pyrrolobenzazepines **14a**,**15a** in good yields (65–80%, Scheme 3). Compounds



Scheme 3. *X*=**14**: CN; **15**: COOEt. *n*=**a**: 1; **b**: 2; **c**: 3.

14a,**15a** were assumed to be formed at the expense of another sigmatropic process. Thus, the initial bipolar intermediate **12** underwent hydrogen 1,3-shift leading to further intermediate **13** with endocyclic double bond. Its ring closure furnished derivatives **14a**,**15a**. In the case of six and seven member amines **10b**,**c**, **11b**,**c** (or **8b**,**c**, **9b**,**c**) the similar transformation appeared to occur significantly worse. Nevertheless, the corresponding fused benzazepines **14b**,**c**, **15b**,**c** were obtained, but in poor yields (10–20%). Perhaps enlarging of the ring size led to a less favorable endocyclic double bond, thus increasing energy of the intermediate **13** comparing to **12** and hampering the reaction.

Formation of the fused benzazepines **14**,**15** can be considered as the hitherto unknown formal homologous variant of the typical *tert*-amino effect. Also it provides a facile route to pyrrolo[1,2-*b*][2]benzazepines **14a**,**15a**. The previously known approaches to this heterocyclic core utilized intramolecular rearrangements of certain azido and diazo compounds,[38–40] intramolecular Heck reactions of suitable pyrrolidine derivatives,[41,42] and photochemical transformations of *N*-(4-pentenyl)phthalimides.[43–47] Furthermore, a few less general methods have been reported.[48–51]

The structures of the prepared compounds **14**,**15** were confirmed by ^{1}H and ^{13}C NMR data. Moreover, in the case of the esters **11a**–**c** the reaction turned out to occur diastereoselectively yielding the products **15a**–**c** with definite relative configuration of the two neighboring stereocenters. So, in order to assign the relative stereochemistry and to confirm the structure surely an X-ray crystallographic study was performed for the derivative **15a** (Fig. 1). It revealed clearly the *cis* mutual arrangement of the bridgehead hydrogen atom and the ester group. Following the analogy the same relative configuration was assigned throughout the series of compounds **15a**–**c**. Thus, they should be formulated as the racemates of the pair of enantiomeric structures **A** and **B** (Fig. 2).

According to the crystal data the azepine ring adopts a chair conformation with the coplanar atoms C(1), N(1), C(8), and C(9) (with precision of 0.04 Å) and the atoms C(2), C(7), and C(10) deviated from their plane at +0.99 Å,+1.04 Å, and −0.71 Å, respectively. Simultaneously the pyrrolidine ring has asymmetric twist conformation with the N(1) and C(10) atoms deviated from the least-squared plane of the rest of the atoms of the ring at +0.71 Å and +0.22 Å, correspondingly.

To resume, the present investigation has resulted in discovery of the novel type of the *tert*-amino effect reaction. Formally it looks like the well known *tert*-amino effect process (Scheme 1) simply extended to the homologous compounds **8**,**9**. However, actually the overall transformation of derivatives **8**,**9** into benzazepines **14**,**15** has been shown to include the sequence of two reactions proceeding through the bipolar intermediates **12** and **13**. Characterization of the indanes **10**,**11** has provided sufficient proof for this

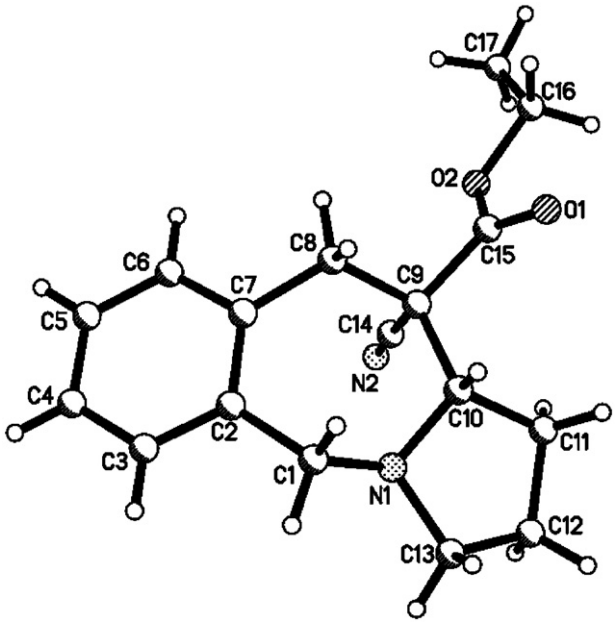


Fig. 1. X-ray molecular structure of compound **15a** with the atom numbering used in the crystallographic analysis.

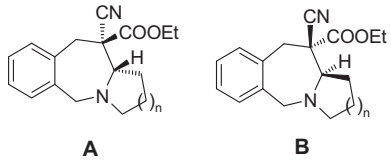


Fig. 2. The relative configuration of compounds **15a**–**c**.

assumption. Furthermore the reaction found has a practical aspect. Thus, it enables the effortless preparation of hydrogenated fused 2-benzazepines, the family of relatively rare heterocycles interesting for medicinal chemistry.[38–47] So, the further research on the scope and synthetic applications of the homologous *tert*-amino effect is in progress.

3. Experimental

3.1. General

Cinnamonitriles **5**,**6**[25] and aldehydes **7a**,**b**[26,27] were prepared according to the described procedures. Other reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts (δ) are given in parts per million downfield from internal Me_4Si. J values are in hertz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

3.2. 2-(Azepan-1-ylmethyl)benzaldehyde (7c)

n-Butyllithium (125 mL, 1,6 M solution in hexane) was added dropwise to a stirred solution of 1-benzylazepane (18.9 g, 0.1 mol) in anhydrous ether (100 mL) under argon atmosphere at 0 °C and resulting mixture was stirred at rt for 2 days. Then it was cooled to 0 °C and anhydrous DMF (13.1 mL) was added dropwise and the stirring was continued for 8 h. The mixture was poured onto crushed ice (200 g) and concd hydrochloric acid (25 mL) was added. The organic layer was separated and the water solution was washed with ether (2×100 mL). The aqueous phase was neutralized with NaOH and extracted with ether (3×100 mL). The extract was dried (Na_2SO_4), the solvent was evaporated, and the residue was distilled yielding the aldehyde **7c** (13.69 g, 63%) as a yellowish liquid, bp 120–125 °C/3 mmHg δ_H ($CDCl_3$) 1.59 (8H, m, $4CH_2$), 2.63 (4H, m, $2NCH_2$), 3.91 (2H, s, CH_2), 7.38 (2H, m, 3,4-H), 7.49 (1H, t, J=7.0 Hz, 5-H), 7.86 (1H, d, J=7.0 Hz, 6-H), 10.47 (1H, s, CHO). δ_C ($CDCl_3$) 26.9, 28.4, 55.0, 59.8, 127.5, 128.7, 130.1, 132.9, 135.5, 142.8, 192.3. ν_{max}(KBr) 2923, 1689, 1587, 1260, 1223, 1210, 1094, 1018, 767 cm^{-1}. Found: C, 77.31; H, 8.88; N, 6.41. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45.

3.3. Cinnamonitriles 8a–c, 9a–c and indanes 10a–c, 11a–c. General procedure

3.3.1. Route A. An appropriate amine (0.021 mol) was added to the ice-cooled and stirred solution of compounds **5**,**6** (0.01 mol) in EtOH (25 mL) and resulting mixture was stirred at room temperature overnight. Then it was poured into water (100 mL), the solid formed was filtered and recrystallized from a suitable solvent to give derivatives **8a**–**c**, **9a**–**c** (if the spectra were recorded in $CDCl_3$) or **10a**–**c**, **11a**–**c** (if the spectra were recorded in DMSO-d_6). During the recrystallization prolonged heating should be avoided.

3.3.2. Route B. Malononitrile or ethyl cyanoacetate (0.01 mol) was added to a solution of the aldehydes **7a**–**c** (0.01 mol) in EtOH (20 mL) and the mixture obtained was left overnight at room temperature. Then it was worked up as above yielding derivatives **8a**–**c**, **9a**–**c** or **10a**–**c**, **11a**–**c** dependent on the solvent where the spectra were recorded.

*3.3.3. [2-(Pyrrolidin-1-ylmethyl)benzylidene]-malononitrile (**8a**).* Yield 2.18 g, 92% via route A; 2.13 g, 90% via route B. Yellow powder; mp 128–130 °C (from *i*-PrOH). δ_H ($CDCl_3$) 1.94 (4H, m, $2CH_2$), 2.82 (4H, m, $2NCH_2$), 3.96 (2H, s, NCH_2), 7.30 (1H, d, J=7.0 Hz, 3-H), 7.43 (2H, m, 4,5-H), 7.58 (1H, s, CH), 7.77 (1H, d, J=7.0 Hz, 6-H). δ_C ($CDCl_3$) 23.2, 54.3, 59.7, 94.4, 116.4, 116.9, 128.0, 128.1, 128.2, 128.6, 131.8, 132.2, 144.8. ν_{max}(KBr) 2176, 2133, 1459, 1440, 1367, 1331, 1274, 798, 755, 731, 670 cm^{-1}. Found: C, 76.14; H, 6.57; N, 17.71. $C_{15}H_{15}N_3$ requires C, 75.92; H, 6.37; N, 17.71.

*3.3.4. [2-(Piperidin-1-ylmethyl)benzylidene]-malononitrile (**8b**).* Yield 2.16 g, 86% via route A; 2.31 g, 92% via route B. Yellow powder; mp 105–107 °C; (from MeOH). δ_H ($CDCl_3$) 1.51 (2H, m, CH_2), 1.59 (4H, m, $2CH_2$), 2.47 (4H, m, $2NCH_2$), 3.63 (2H, s, NCH_2), 7.30 (1H, t, J=7.5 Hz, 5-H), 7.42–7.49 (2H, m, 3,4-H), 7.90 (1H, d, J=7.5 Hz, 6-H), 8.29 (1H, s, CH). δ_C ($CDCl_3$) 24.2, 25.8, 54.0, 62.3, 94.4, 116.4, 116.8, 128.0, 128.1, 128.2, 128.6, 131.7, 132.2, 144.8. ν_{max}(KBr) 2979, 2157, 1636, 1452, 1392, 1375, 1270, 1249, 1093, 761, 740, 675 cm^{-1}. Found: C, 76.63; H, 6.82; N, 16.75. $C_{16}H_{17}N_3$ requires C, 76.46; H, 6.82; N, 16.72.

*3.3.5. [2-(Azepan-1-ylmethyl)benzylidene]-malononitrile (**8c**).* Yield 2.07 g, 78% via route A; 2.01 g, 76% via route B. Yellow powder; mp 76 °C; (from MeOH). δ_H ($CDCl_3$) 1.64 (8H, m, $4CH_2$), 2.66 (4H, m, $2NCH_2$), 3.75 (2H, s, NCH_2), 7.30 (1H, d, J=7.5 Hz, 3-H), 7.43 (1H, t, J=7.5 Hz, 5-H), 7.48 (1H, t, J=7.5 Hz, 4-H), 7.91, (1H, d, J=7.5 Hz, 6-H), 8.38 (1H, s, CH). δ_C ($CDCl_3$) 26.9, 28.0, 54.9, 61.2, 89.7, 113.5, 116.0, 128.2, 128.8, 129.7, 131.1, 132.6, 141.1, 159.3. ν_{max}(KBr) 2918, 2849, 2176, 2139, 1736, 1593, 1538, 1471, 1452, 1355, 1279, 1219, 1177, 934, 796, 761, 729 cm^{-1}. Found: C, 76.75; H, 7.47; N, 15.74. $C_{17}H_{19}N_3$ requires C, 76.95; H, 7.22; N, 15.84.

*3.3.6. Ethyl 2-cyano-3-[2-(pyrrolidin-1-ylmethyl)phenyl]acrylate (**9a**).* Yield 2.75 g, 97% via route A; 2.41 g, 85% via route B. Yellow powder; mp 102–104 °C; (from *i*-PrOH). δ_H ($CDCl_3$) 1.39 (3H, t,

J=7.0 Hz, CH_3), 1.78 (4H, m, $2CH_2$), 2.60 (4H, m, $2NCH_2$), 3.79 (2H, s, NCH_2), 4.35 (2H, q, J=7.0 Hz, OCH_2), 7.33 (1H, d, J=7.5 Hz, 3-H), 7.41 (2H, m, 4,5-H), 8.02 (1H, d, J=7.5 Hz, 6-H), 8.67 (1H, s, CH). δ_C ($CDCl_3$) 14.2, 23.6, 53.9, 58.8, 62.1, 98.9, 116.3, 127.9, 128.6, 129.3, 131.7, 131.8, 140.6, 151.0, 163.4. ν_{max}(KBr) 2973, 2895, 2161, 1734, 1634, 1441, 1376, 1343, 1267, 1248, 1084, 801, 759, 745, 657 cm^{-1}. Found: C, 71.74; H, 7.05; N, 9.80. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.85.

*3.3.7. Ethyl 2-cyano-3-[2-(piperidin-1-ylmethyl)phenyl]acrylate (**9b**).* Yield 2.86 g, 96% via route A; 2.83 g, 95% via route B. Pale yellow powder; mp 55 °C; (from MeOH). δ_H ($CDCl_3$) 1.43 (5H, m, CH_3, CH_2), 1.52 (4H, m, $2CH_2$), 2.41 (4H, m, $2NCH_2$), 3.57 (2H, s, NCH_2), 4.40 (2H, q, J=7.0 Hz, OCH_2), 7.31 (1H, d, J=7.0 Hz, 3-H), 7.42 (2H, m, 4,5-H), 8.07 (1H, d, J=7.0 Hz, 6-H), 8.89 (1H, s, CH). δ_C ($CDCl_3$) 14.2, 24.2, 25.8, 54.0, 62.0, 62.3, 101.0, 116.0, 127.9, 128.9, 130.1, 131.6, 131.8, 140.4, 154.6, 163.0. ν_{max}(KBr) 2965, 2176, 2133, 1736, 1480, 1459, 1371, 1309, 1288, 1249, 1029, 777, 752, 717, 689 cm^{-1}. Found: C, 72.59; H, 7.50; N, 9.27. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39.

*3.3.8. Ethyl 3-[2-(azepan-1-ylmethyl)phenyl]-2-cyanoacrylate (**9c**).* Compound **9c** was separated as oil after the aqueous work up. It was taken up in ethyl acetate (20 mL), washed with water (2×10 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography on silica gel with ethyl acetate–hexane (1:4, v/v; R_f 0.76) mixture as eluent yielding compound **9c**. Yield 2.31 g, 74% via route A; 1.68 g, 54% via route B. Yellow oil. δ_H ($CDCl_3$) 1.42 (3H, t, J=7.0 Hz, CH_3), 1.56 (8H, m, $4CH_2$), 2.61 (4H, m, $2NCH_2$), 3.72 (2H, s, NCH_2), 4.40 (2H, q, J=7.0 Hz, OCH_2), 7.30 (1H d, J=7.0 Hz, 3-H), 7.43 (2H, m, 4,5-H), 8.06 (1H, d, J=7.0 Hz, 6-H), 8.92 (1H, s, CH). δ_C ($CDCl_3$) 14.3, 26.9, 28.4, 54.8, 61.5, 62.3, 101.4, 115.9, 127.9, 129.0, 130.0, 131.6, 131.9, 141.5, 155.6, 163.0. ν_{max}(KBr) 2922, 2858, 2242, 2192, 1739, 1732, 1642, 1454, 1360, 1236, 1163, 1128, 1076, 1050, 955, 893, 857, 757 cm^{-1}. Found: C, 72.97; H, 7.80; N, 8.90. $C_{19}H_{24}N_2O_2$ requires C, 73.05; H, 7.74; N, 8.97.

*3.3.9. 1-(Pyrrolidin-1-yl)indane-2,2-dicarbonitrile (**10a**).* Yield 2.18 g, 92% via route A; 2.13 g, 90% via route B. Yellowish powder; mp 128–130 °C; (from *i*-PrOH). δ_H (DMSO-d_6) 2.12 (4H, m, $2CH_2$), 3.35 (4H, m, $2NCH_2$), 4.59 (2H, s, 3-CH_2), 5.94 (1H, s, 1-H), 7.35 (2H, m, 5,6-H), 7.42 (2H, m, 4,7-H). δ_C (DMSO-d_6) 21.9, 40.6, 56.9, 62.7, 90.3, 124.0, 125.2, 126.0, 126.1, 129.0, 129.5, 134.6, 136.2. ν_{max}(KBr) 2176, 2133, 1459, 1440, 1367, 1331, 1274, 798, 755, 731, 670 cm^{-1}. Found: C, 76.14; H, 6.57; N, 17.71. $C_{15}H_{15}N_3$ requires C, 75.92; H, 6.37; N, 17.71.

*3.3.10. 1-(Piperidin-1-yl)indane-2,2-dicarbonitrile (**10b**).* Yield 2.16 g, 86% via route A; 2.31 g, 92% via route B. Yellowish powder; mp 105–107 °C; (from MeOH). δ_H (DMSO-d_6) 1.61 (2H, m, CH_2), 1.82 (4H, m, $2CH_2$), 3.04 (4H, m, $2NCH_2$), 4.57 (2H, s, 3-CH_2), 6.06 (1H, s, 1-H), 7.38 (2H, m, 5,6-H), 7.44 (2H, m, 4,7-H). δ_C (DMSO-d_6) 21.5, 22.1, 39.6, 40.5, 53.5, 58.6, 116.2, 117.3, 124.8, 125.8, 128.0, 129.9, 134.7, 135.1. ν_{max}(KBr) 2979, 2157, 1636, 1452, 1392, 1375, 1270, 1249, 1093, 761, 740, 675 cm^{-1}. Found: C, 76.63; H, 6.82; N, 16.75. $C_{16}H_{17}N_3$ requires C, 76.46; H, 6.82; N, 16.72.

*3.3.11. 1-(Azepan-1-yl)indane-2,2-dicarbonitrile (**10c**).* Yield 2.07 g, 78% via route A; 2.01 g, 76% via route B. Yellowish powder; mp 76 °C; (from MeOH). δ_H (DMSO-d_6) 1.65 (4H, m, $2CH_2$), 1.84 (4H, m, $2CH_2$), 3.20 (4H, m, $2NCH_2$), 4.43 (2H, s, 3-CH_2), 6.44 (1H, s, 1-H), 7.38 (2H, m, 5,6-H), 7.43 (2H, m, 4,7-H). δ_C (DMSO-d_6) 24.2, 27.3, 27.4, 40.6, 57.0, 61.6, 125.5, 126.3, 127.8, 128.4, 128.8, 130.3, 134.9, 136.3. ν_{max}(KBr) 2918, 2849, 2176, 2139, 1736, 1593, 1538, 1471, 1452, 1355, 1279, 1219, 1177, 934, 796, 761, 729 cm^{-1}. Found: C, 76.75; H, 7.47; N, 15.74. $C_{17}H_{19}N_3$ requires C, 76.95; H, 7.22; N, 15.84.

*3.3.12. Ethyl 2-cyano-1-(pyrrolidin-1-yl)indane-2-carboxylate (**11a**).* Yield 2.75 g, 97% via route A; 2.41 g, 85% via route B. Yellow powder; mp 102–104 °C; (from *i*-PrOH). δ_H (DMSO-d_6) 1.18 (3H, t, J=7.0 Hz, CH_3), 2.02 (4H, m, $2CH_2$), 3.25 (4H, m, $2NCH_2$), 4.01 (2H, q, J=7.0 Hz, OCH_2), 4.55 (2H, s, 3-CH_2), 6.47 (1H, s, 1-H), 7.30–7.41 (4H, m, 4,5,6,7-H). δ_C (DMSO-d_6) 15.4, 22.2, 40.6, 56.5, 58.6, 62.3, 98.2, 124.3, 124.8, 125.6, 128.7, 129.5, 135.8, 136.5, 169.5. ν_{max}(KBr) 2973, 2895, 2161, 1734, 1634, 1441, 1376, 1343, 1267, 1248, 1084, 801, 759, 745, 657 cm^{-1}. Found: C, 71.74; H, 7.05; N, 9.80. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.85.

*3.3.13. Ethyl 2-cyano-1-(piperidin-1-yl)indane-2-carboxylate (**11b**).* Yield 2.86 g, 96% via route A; 2.83 g, 95% via route B. Pale yellow powder; mp 55 °C; (from MeOH). δ_H (DMSO-d_6) 1.25 (3H, t, J=7.5 Hz, CH_3), 1.45 (2H, m, CH_2), 1.60 (4H, m, $2CH_2$), 2.69 (4H, m, $2NCH_2$), 4.13 (2H, s, 3-CH_2), 4.16 (2H, q, J=7.5 Hz, OCH_2), 7.37, (1H, d, J=6.5 Hz, 4-H), 7.44 (2H, m, 5,6-H), 7.53 (1H, s, 1-H), 7.57 (1H, d, J=6.5 Hz, 7-H). δ_C (DMSO-d_6) 15.0, 23.1, 23.8, 40.7, 53.9, 60.3, 60.6, 89.8, 120.4, 127.4, 127.8, 128.4, 130.8, 133.8, 138.3, 166.1. ν_{max}(KBr) 2965, 2176, 2133, 1736, 1480, 1459, 1371, 1309, 1288, 1249, 1029, 777, 752, 717, 689 cm^{-1}. Found: C, 72.59; H, 7.50; N, 9.27. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39.

*3.3.14. Ethyl 1-(azepan-1-yl)-2-cyanoindane-2-carboxylate (**11c**).* Compound **11c** was separated as oil after the aqueous work up. It was taken up in ethyl acetate (20 mL), washed with water (2×10 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography on silica gel with ethyl acetate–hexane (1:4, v/v; R_f 0.76) mixture as eluent yielding compound **11c**. Yield 2.31 g, 74% via route A; 1.68 g, 54% via route B. Yellow oil. δ_H (DMSO-d_6) 1.25 (3H, t, J=7.0 Hz, CH_3), 1.65 (4H, m, $2CH_2$), 1.84 (4H, m, $2CH_2$), 3.21 (4H, m, $2NCH_2$), 4.12–4.18 (4H, m, 3-CH_2, OCH_2), 6.44 (1H, s, 1-H), 7.40 (2H, m, 4,7-H), 7.43 (2H, m, 5,6-H). δ_C (DMSO-d_6) 15.0, 24.2, 27.4, 40.7, 53.9, 60.3, 60.6, 89.8, 120.4, 127.4, 127.8, 128.4, 130.8, 133.8, 138.3, 166.1. ν_{max}(KBr) 2922, 2858, 2242, 2192, 1739, 1732, 1642, 1454, 1360, 1236, 1163, 1128, 1076, 1050, 955, 893, 857, 757 cm^{-1}. Found: C, 72.97; H, 7.80; N, 8.90. $C_{19}H_{24}N_2O_2$ requires C, 73.05; H, 7.74; N, 8.97.

3.4. Pyrrolo[1,2-*b*][2]benzazepines 14a,15a. General procedure

A solution of appropriate indane **10a**,**11a** (5 mmol) in DMSO (15 mL) was heated at 140–150 °C for 2 h. Upon cooling the solvent was evaporated in vacuo, the residue was triturated with water, filtered, and recrystallized from *i*-PrOH yielding compounds **14a**,**15a**.

*3.4.1. 1,2,3,5,10,11a-hexahydro-11H-pyrrolo[1,2-b][2]benzazepine-11,11-dicarbonitrile (**14a**).* Yield 0.95 g, 80%. White powder; mp 99 °C δ_H ($CDCl_3$) 1.92 (1H, m, 1-H), 2.03–2.17 (2H, m, 1,2-H), 2.40 (1H, m, 2-H), 2.73 (1H, m, 11a-H), 3.16 (1H, m, 3-H), 3.33 (1H, m, 3-H), 3.48 (1H, d, J=14.5 Hz, 10-H), 3.58 (1H, d, J=14.5 Hz, 10-H), 3.84 (1H, d, J=14.5 Hz, 5-H), 4.10 (1H, d, J=14.5 Hz, 5-H), 7.22 (1H, d, J=6.5 Hz, 6-H), 7.29–7.33 (3H, m, 7,8,9-H). δ_C ($CDCl_3$) 22.0, 30.8, 40.8, 42.3, 56.0, 58.7, 71.5, 113.6, 115.5, 128.1, 128.8, 129.0, 131.4, 132.0, 138.9. ν_{max}(KBr) 2960, 2844, 1457, 1443, 1397, 1272, 1263, 1221, 1191, 1142, 1101, 1086, 1036, 1022, 793, 777, 761, 729 cm^{-1}. Found: C, 75.74; H, 6.28; N, 17.77. $C_{15}H_{15}N_3$ requires C, 75.92; H, 6.37; N, 17.71.

*3.4.2. Ethyl 11-cyano-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[1,2-b][2]benzazepine-11-carboxylate (**15a**).* Yield 0.92 g, 65%. White crystals; mp 87 °C δ_H ($CDCl_3$) 1.37 (3H, t, J=7.0 Hz, CH_3), 1.77 (1H, m, 1-H), 1.92 (2H, m, 1,2-H), 2.01 (1H, m, 2-H), 2.61 (1H, m, 11a-H), 3.02 (1H, m, 3-H), 3.14 (1H, d, J=14.5 Hz, 10-H), 3.30 (1H, m, 3-H), 3.50 (1H, d, J=14.5 Hz, 10-H), 3.73, (1H, d, J=14.5 Hz, 5-H), 3.92 (1H, d, J=14.5 Hz, 5-H), 4.32 (2H, m, OCH_2), 7.21–7.27 (4H, m, 6,7,8,9-H). δ_C ($CDCl_3$) 14.1, 21.3, 29.8, 41.7, 53.0, 56.4, 59.3, 62.8, 72.5, 116.7, 127.7, 128.0, 129.1, 131.0, 134.6, 139.1, 168.1. ν_{max}(KBr) 2939, 2833, 2793,

1737, 1460, 1444, 1246, 1151, 1095, 1038, 1010, 771 cm^{-1}. Found: C, 71.80; H, 7.10; N, 9.83. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.85.

3.5. Pyrido[1,2-*b*][2]benzazepines 14b, 15b and Azepino[1,2-*b*][2]benzazepines 14c, 15c. General procedure

A solution of appropriate indane **10b**,**c**, **11b**,**c** (5 mmol) in DMSO (15 mL) was heated at 140–150 °C for 2 h. After cooling the solvent was evaporated in vacuo, the residue was treated with hot heptane and insoluble materials were removed by filtration. The heptane filtrate was concentrated in vacuo and the residue was subjected to column chromatography on silica gel using ethyl acetate–hexane (1:4, v/v) mixture as eluent yielding compounds **14b**,**c**, **15b**,**c**.

*3.5.1. 1,3,4,6,11,12a-Hexahydropyrido[1,2-b][2]benzazepine-12,12(2H)-dicarbonitrile (**14b**).* Yield 0.15 g, 12%. White solid; mp 112 °C. R_f (25% EtOAc/hexane) 0.64. δ_H ($CDCl_3$) 1.59 (1H, m, 2-H), 1.68 (2H, m, 1,2-H), 2.02 (2H, m, 1,3-H), 2.24 (1H, m, 3-H), 2.48 (1H, m, 4-H), 3.01 (1H, m, 4-H), 3.11 (1H, m, 12a-H), 3.47 (1H, d, J=14.0 Hz, 11-H), 3.75 (2H, m, 6,11-H), 3.97 (1H, d, J=14.0 Hz, 6-H), 7.24 (1H, m, 10-H), 7.33 (3H, m, 7,8,9-H). δ_C ($CDCl_3$) 21.1, 25.1, 28.6, 30.6, 39.8, 43.3, 52.8, 62.1, 114.3, 116.2, 128.3, 128.8, 129.4, 130.5, 133.1, 138.7. ν_{max}(KBr) 2951, 2812, 2779, 2232, 1731, 1591, 1457, 1286, 1247, 1223, 1080, 1057, 766, 731 cm^{-1}. Found: C, 76.50; H, 6.76; N, 16.81. $C_{16}H_{17}N_3$ requires C, 76.46; H, 6.82; N, 16.72.

*3.5.2. 5,7,8,9,10,11,11a,13-octahydro-12H-azepino[1,2-b][2]benzazepine-12,12-dicarbonitrile (**14c**).* Yield 0.25 g, 19%. White solid; mp 137 °C. R_f (25% EtOAc/hexane) 0.79. δ_H ($CDCl_3$) 1.33 (1H, m, 9-H), 1.44–1.58 (3H, m, 9,10,10-H), 1.89–2.01 (3H, m, 8,8,11-H), 2.44 (1H, m, 11-H), 2.76 (1H, m, 7-H), 3.19 (1H, m, 11a-H), 3.48 (2H, m, 7,13-H), 3.65 (1H, d, J=14.0 Hz, 13-H), 4.08 (1H, d, J=15.0 Hz, 5-H), 4.23 (1H, d, J=15.0 Hz, 5-H), 7.19 (1H, m, 1H), 7.30 (3H, m, 2,3,4-H). δ_C ($CDCl_3$) 26.2, 28.3, 29.8, 32.0, 39.7, 42.4, 47.7, 59.2, 70.3, 115.0, 115.9, 127.9, 128.3, 128.6, 131.4, 132.2, 139.6. ν_{max}(KBr) 2946, 2918, 2839, 2237, 1736, 1445, 1399, 1367, 1237, 1161, 1124, 955, 939, 886, 761, 746, 699 cm^{-1}. Found: C, 77.04; H, 6.99; N, 15.61. $C_{17}H_{19}N_3$ requires C, 76.95; H, 7.22; N, 15.84.

*3.5.3. Ethyl 12-cyano-1,2,3,4,6,11,12,12a-octahydro-pyrido[1,2-b][2]benzazepine-12-carboxylate (**15b**).* Yield 0.16 g, 11%. Pale yellow oil. R_f (25% EtOAc/hexane) 0.70.δ_H ($CDCl_3$) 1.40 (4H, m, 2-H, CH_3), 1.68 (4H, m, 1,2,3,3-H), 1.90 (1H, m, 1-H), 2.45 (1H, m, 4-H), 3.03–3.12 (3H, m, 4,11,12a-H), 3.69 (2H, m, 6,11-H), 3.97 (1H, d, J=15.0 Hz, 6-H), 4.35 (2H, m, OCH_2), 7.23–7.29 (4H, m, 7,8,9,10-H). δ_C ($CDCl_3$) 14.1, 21.8, 25.5, 30.3, 42.2, 52.6, 54.3, 62.7, 62.9, 69.1, 117.8, 128.0, 128.1, 129.3, 130.1, 135.4, 138.7, 168.8. ν_{max}(KBr) 2946, 2932, 2849, 2176, 2135, 1460, 1441, 1318, 1283, 1146, 1105, 1078, 990, 752, 704, 652 cm^{-1}. Found: C, 72.27; H, 7.23; N, 9.27. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39.

*3.5.4. Ethyl 12-cyano-7,8,9,10,11,11a,12,13-octahydro-5H-azepino[1,2-b][2]benzazepine-12-carboxylate (**15c**).* Yield 0.19 g, 12%. White solid; mp 91 °C. R_f (25% EtOAc/hexane) 0.68. δ_H ($CDCl_3$) 1.25 (1H, m, 9-H), 1.38 (4H, m, 9-H, CH_3), 1.53 (2H, m, 10-CH_2), 1.85 (4H, m, 8,11-CH_2), 2.58 (1H, m, 7-H), 3.13 (2H, m, 11a,13-H), 3.61–3.69 (2H, m, 7,13-H), 3.94 (1H, d, J=15.0 Hz, 5-H), 4.20 (1H, d, J=15.0 Hz, 5-H), 4.31 (2H, m, OCH_2), 7.17 (1H, m, 2-H), 7.26 (3H, m, 1,3,4-H). δ_C ($CDCl_3$) 14.1, 21.2, 29.7, 29.8, 41.7, 53.0, 56.4, 59.3, 62.9, 72.5, 72.6, 116.7, 127.8, 128.1, 129.1, 131.0, 134.6, 139.0, 168.1. ν_{max}(KBr) 2937, 2834, 2793, 1735, 1459, 1443, 1244, 1149, 1094, 1057, 1036, 1008, 860, 770, 708 cm^{-1}. Found: C, 73.25; H, 7.62; N, 9.14. $C_{19}H_{24}N_2O_2$ requires C, 73.05; H, 7.74; N, 8.97.

3.6. X-ray crystal structure determination of compound 15a

Intensities of 9226 reflections (4226 independent, R_{int}=0.026) were measured with 'Xcalibur-3' diffractometer operating in the ω-2θ scan mode, $2\theta_{max}$=60°, and using graphite monochromated Mo Kα radiation (λ=0.71073 Å). Crystal data: $C_{17}H_{20}N_2O_2$, M_r=284.35, orthorhomibc, a=13.552 Å, b=9.678 Å, c=11.630 Å, V=1525.4 $Å^3$, T=293 K, space group $Pna2_1$, Z=4, μ(Mo Kα)=0.082 mm^{-1}. The structure was solved by direct method with the SHELXTL program package.[52] Positions of hydrogen atoms were located from electron difference density maps and refined isotropically. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 4186 reflections was converged to wR_2=0.076, R_1=0.036 [for 2830 reflections with $F>4\sigma(F)$], S=0.865. Full crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 781983. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Supplementary data

^1H and ^{13}C NMR spectra of all compounds obtained are available in pdf file format as the Supplementary data. Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.11.101. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269–276.
2. Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 3136–3138.
3. Groenen, L. C.; Verboom, W.; Nijhuis, W. H. N.; Reinhoudt, D. N.; van Hummel, G. J.; Feil, D. *Tetrahedron* **1988**, *44*, 4637–4644.
4. Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199–208.
5. Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; van Hummel, G. J.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 209–216.
6. Kelderman, E.; Noorlander-Bunt, H. G.; Van Eerden, J.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 115–123.
7. Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311–324.
8. Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211–278.
9. Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1987**, 641–645.
10. Nijhuis, W. H. N.; Leus, G. R. B.; Egberink, R. J. M.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 172–178.
11. Gerlach, U. *Tetrahedron Lett.* **1995**, *36*, 5159–5162.
12. Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Tetrahedron* **2006**, *62*, 9146–9152.
13. Glukhareva, T. V.; Dyachenko, E. V.; Morzherin, Y. Y. *Khim. Geterotsikl. Soedin.* **2002**, 1610–1611; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 1426–1427.
14. Dyachenko, E. V.; Glukhareva, T. V.; Morzherin, Y. Y. *Khim. Geterotsikl. Soedin.* **2003**, 1737–1738; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, *39*, 1532–1533.
15. Dyachenko, E. V.; Glukhareva, T. V.; Nikolaenko, E. F.; Tkachev, A. V.; Morzherin, Y. Y. *Izv. Akad. Nauk, Ser. Khim.* **2004**, *53*, 1191–1198; *Russ. Chem. Bull.* **2004**, *53*, 1240–1247.
16. Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Synthesis* **2005**, 2161–2170.
17. Ojea, V.; Peinador, C.; Quintela, J. M. *Synthesis* **1992**, 798–802.
18. Ojea, V.; Peinador, C.; Vilar, J.; Quintela, J. M. *Synthesis* **1993**, 152–157.
19. Verboom, W.; Verboom, C.; Eissink, I. M.; Lammerink, B. H. M.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 481–484.
20. Rabong, C.; Hamenter, C.; Mereiter, K.; Kartsev, V. G.; Jordis, U. *Heterocycles* **2008**, *75*, 799–838.
21. Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625–2639.
22. Polonka-Balint, A.; Saraceno, C.; Ludanyi, K.; Benyei, A.; Matyus, P. *Synlett* **2008**, 2846–2850.
23. Dunkel, P.; Turos, G.; Benyei, A.; Ludanyi, K.; Mátyus, P. *Tetrahedron* **2010**, *66*, 2331–2339.
24. Földi, A. A.; Ludanyi, K.; Benyei, A. C.; Mátyus, P. *Synlett* **2010**, 2109–2113.
25. Kolsaker, P.; Ellingsen, P. O. *Acta Chem. Scand.* **1979**, *33B*, 138–140.
26. Wayman, K. A.; Sammakia, T. *Org. Lett.* **2003**, *5*, 4105–4108.
27. Bentley, R. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1725–1734.
28. Zhu, X.-Q.; Wang, H.-Y.; Wang, J.-S.; Liu, Y.-C. *J. Org. Chem.* **2001**, *66*, 344–347.
29. Wang, H.; Dai, D.; Liu, Y.; Guo, Q. *Tetrahedron Lett.* **2002**, *43*, 7527–7530.
30. Zhang, B.; Zhu, X.-Q.; Lu, J.-Y.; He, J.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2003**, *68*, 3295–3298.
31. Kolsaker, P.; Hellebostad, K. *Acta Chem. Scand.* **1980**, *34B*, 721–729.

32. Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Organomet. Chem.* **2007**, *692*, 625–634.
33. Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018–8020.
34. Negishi, E.; Makabe, H.; Shimoyama, I.; Wu, G.; Zhang, Y. *Tetrahedron* **1998**, *54*, 1095–1106.
35. Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428–9438.
36. Taylor, J. B.; Lewis, J. W.; Jacklin, M. *J. Med. Chem.* **1970**, *13*, 1226–1227.
37. Ridvan, L.; Zavada, J. *Tetrahedron* **1997**, *53*, 14793–14806.
38. Mossman, C. J.; Aube, J. *Tetrahedron* **1996**, *52*, 3403–3408.
39. Milligan, G. L.; Mossman, C. J.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.
40. Muroni, D.; Mucedda, M.; Saba, A. *Tetrahedron: Asymmetry* **2009**, *20*, 1154–1159.
41. Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87–93.
42. Ikeda, M.; Akamatsu, S.; Kugo, Y.; Sato, T. *Heterocycles* **1996**, *42*, 155–158.
43. Mazzocchi, P. H.; DeCamp Shuda, A. *Heterocycles* **1985**, *23*, 1603–1606.
44. Weidner-Wells, M. A.; DeCamp, A.; Mazzocchi, P. H. *J. Org. Chem.* **1989**, *54*, 5746–5758.
45. Maruyama, K.; Kubo, Y. *Chem. Lett.* **1978**, 769–772.
46. Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981–2989.
47. Maruyama, K.; Ogawa, T.; Kubo, Y.; Araki, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2025–2032.
48. Reinhard, R.; Glaser, M.; Neumann, R.; Maas, G. *J. Org. Chem.* **1997**, *62*, 7744–7751.
49. Leonard, N. J.; Swann, S.; Fuller, G. *J. Am. Chem. Soc.* **1954**, *76*, 3193–3197.
50. Leonard, N. J.; Wildman, W. C. *J. Am. Chem. Soc.* **1949**, *71*, 3089–3093.
51. Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1985**, *26*, 4115–4118.
52. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.