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Enantioselective syntheses and X-ray structures of (*S*)- and (*R*)-*N*-norlaudanidine: trace opium constituents

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ABSTRACT

The enantioselective synthesis of each of the enantiomers of *N*-norlaudanidine, a minor *Papaver somniferum* opium benzyltetrahydoisoquinoline alkaloid is described. This was achieved using a chiral auxiliary-mediated Bischler–Napieralski cyclization-sodium borohydride reduction strategy. The X-ray crystal structures of each of these secondary amines are reported.

1. Introduction

Benzyltetrahydroisoquinolines ('BTHIQ') which contain a B ring that is reduced at the C1–C2 and C3–C4 positions are known to be key biosynthetic precursors to many naturally occurring alkaloids. These include morphine and codeine which are found in, or are derived from, the opium poppy *Papaver somniferum*.[1–5] The global problem of narcotics abuse, especially involving heroin (**1**) and illegal opium poppy cultivation and processing, has prompted renewed research into the analytical chemistry of heroin[5,6] which also includes the detection and analysis of the minor BTHIQ constituents. Some of these constituents of interest (Fig. 1) include laudanosine (**2**), reticuline (**3**), codamine (**4**), and laudanine (**5**). Laudanine, which is also known as 'racemic laudanidine', and reticuline occur in both enantiomeric forms in opium.[7] The recent report by Toske et al.,[5] which described the GC–MS analysis of neutral heroin impurities derived from BTHIQs **2**–**5**, piqued our interest in the application of our synthetic methodology toward the enantioselective syntheses of **6a** and **6b**, the (*S*)- and (*R*)-enantiomers of *N*-norlaudanidine (1,2,3,4-tetrahydro-l-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline), respectively, and to unambiguously assign the chirality of these compounds by their optical rotations and X-ray crystallography. To the best of our knowledge, no previous unambiguous direct assignment of these particular compounds has been reported.

(−)-*N*-Norlaudanine is a component part of the pathway for the biosynthesis of the benzylisoquinoline alkaloids in *Papaver somniferum*.[7] It has been found to be incorporated into palaudine, another minor benzylisoquinoline constituent found in opium.[8] The fact that radiolabelled *N*-norlaudanine, whose absolute configuration was not defined by Brochmann–Hannssen and co-workers,[7] was incorporated into palaudine was an evidence that complete methylation was not necessary for dehydrogenation to take place in *Papaver somniferum*. Herein, we report the enantioselective syntheses of (*S*)- and (*R*)-*N*-norlaudanidine (**6a**) and (**6b**), respectively, and also their respective X-ray structures.

2. Results and discussion

The 1960s and 1970s witnessed a great deal of interest and advances in the chemistry and biogenetic aspects of the BTHIQ alkaloids due primarily to their significant and important medicinal and pharmacological activities. The groups of Battersby[9] and Brochmann–Hannssen[7] published a series of papers on the biosynthetic pathways of benzylisoquinolines and BTHIQs, in particular with reference to the opium alkaloids. Many of the structural elucidations were conducted with painstaking degradation studies and correlations with reference compounds whose absolute configurations were unambiguously defined.[10] In many instances,

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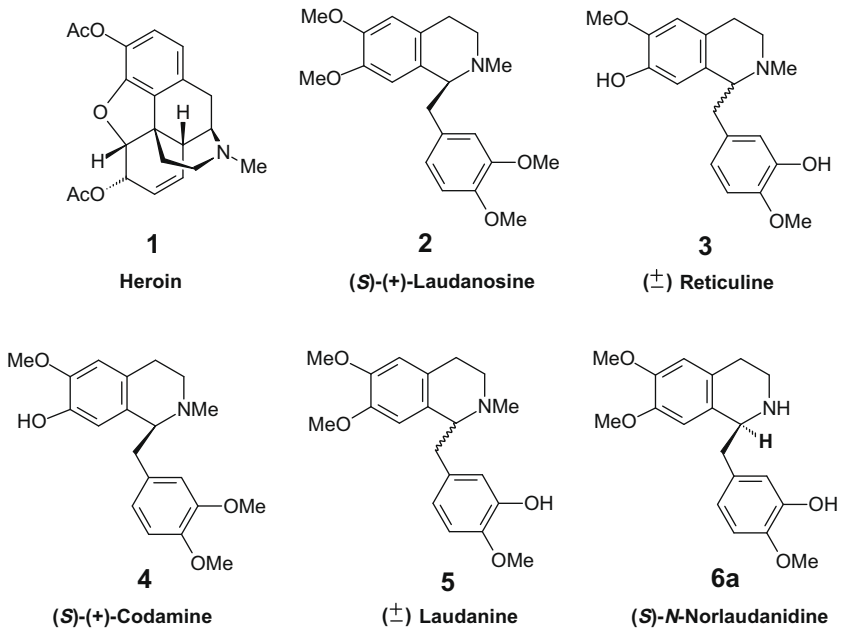
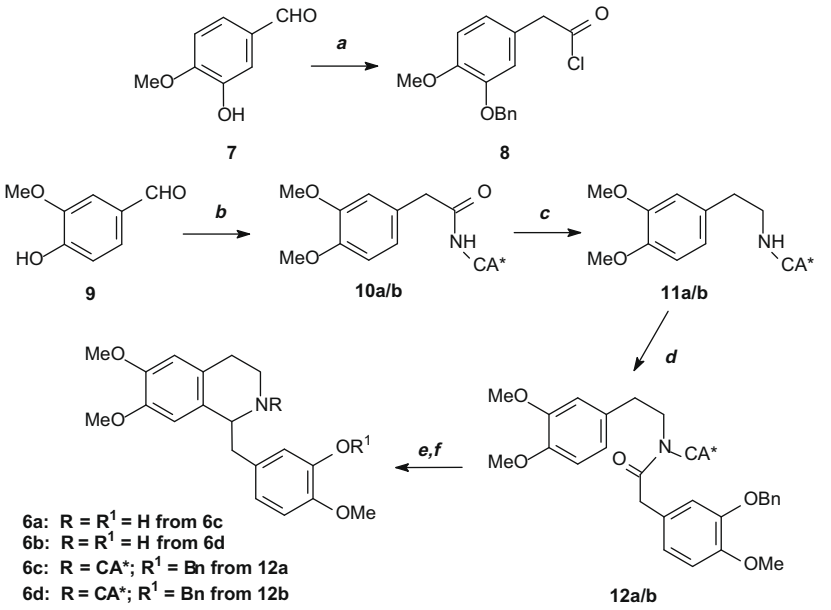


Figure 1. Structures of heroin (**1**) and some BTHIQ alkaloids.

X-ray crystallographic determinations have been obtained on key BTHIQs. In most cases, however, in which total syntheses of target BTHIQs have been reported, the syntheses have yielded only racemic mixtures, even though the chirality of a large number of naturally occurring BTHIQs is due to the presence of only a single stereogenic center at the C-1 position of the tetrahydroisoquinoline unit. In recent years, however, development of new synthetic methodologies has enabled enantioselective syntheses of numerous alkaloids in general, including those which have isoquinoline subunits. A recent example is the enantioselective total synthesis of (*S*)-(+)-laudanosine (**2**) by Mujahidin and Doye, who employed a combination of a Sonogashira coupling reaction, Petasis' reagent, and a Noyori catalyst in their novel approach.[11]

The enantioselective syntheses of BTHIQ and bisbenzyltetrahydroisoquinoline ('BBIQ') alkaloids via the Bischler–Napieralski cyclization reaction in particular have recently been reviewed by Chrzanowska and Rozwadowska.[12a–c] We previously employed the chiral auxiliary (*S*)-α-methylbenzylamine[13] for the first enantioselective synthesis of (−)-tejedine[14] via a Bischler–Napieralski cyclization–reduction sequence which has been frequently employed by others. This is the approach we used in our syntheses of **6a** and **6b** which is outlined below.



Scheme 1. Reagents and conditions: (a) (1) BnBr, DMSO, 98%; (2) CBr_4, PPh_3, CH_2Cl_2, 93%; (3) pyrrolidine, H_2O, rt, 91%; (4) 1.0 M $HCl_{(aq)}$/dioxane; (5) $(COCl)_2$, benzene, 94%. (b) (1) $(CH_3)_2SO_4$, K_2CO_3, acetone, 95%; (2) CBr_4, PPh_3, CH_2Cl_2, 92%; (3) pyrrolidine, H_2O, rt, 91%; 4. 1.0 M $HCl_{(aq)}$/dioxane; (5) $(COCl)_2$, benzene, 96%; (6) CA* = (*S*)- or (*R*)-α-methylbenzylamine, 5% $NaOH_{(aq)}$, CH_2Cl_2, 92%; (c) B_2H_6, THF, $BF_3{\cdot}Et_2O$, 86%; (d) **8**, 5% $NaOH_{(aq)}$, CH_2Cl_2, 72%; (e) (1) $POCl_3$, benzene; (2) $NaBH_4$, MeOH, 89%, (95% de); (f) H_2, 10% Pd/C, EtOH, 10% $HCl_{(aq)}$: **6a** or **6b** ~72%.

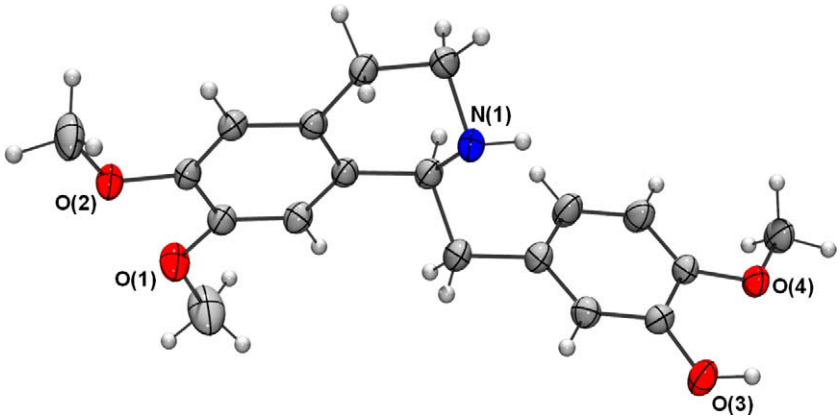


Figure 2. 50% probability ellipsoid ORTEP X-ray structure of **6a**. Solvent benzene molecule omitted for clarity.

2.1. Synthesis

The syntheses of both **6a** and **6b** were accomplished as outlined in Scheme 1 with the only difference being the choice of the chiral auxiliary used within the step *b*: **6a** was obtained using (*S*)-α-methylbenzylamine, and **6b** with (*R*)-α-methylbenzylamine. The benzyl component was synthesized via the intermediate **8** which was obtained in 78% overall yields[15] from 5 steps, starting from the commercially available 3-hydroxy-4-methoxybenzaldehyde (isovanillin) (**7**) which was elongated using the method of Kim et al.[16] Using (*S*)-α-methylbenzylamine as the chiral auxiliary, intermediate **10a** was obtained in 70% overall yields from 6 steps from vanillin (**9**). The corresponding **10b** was obtained in the same manner but using (*R*)-α-methylbenzylamine as the chiral auxiliary. Reduction of **10a** (or **10b**) to the secondary chiral auxiliary-protected amines **11a** (or **11b**) was accomplished in 86% yields via BF_3·etherate-mediated reactions with B_2H_6 in THF. Schotten–Baumann amidation between **11a** (or **11b**) and **8** formed the amides **12a** (or **12b**) in 72% yields. Bischler–Napieralski cyclization-$NaBH_4$ reduction of **12a** and **12b** afforded **6c** and **6d,** respectively, with ~95% de, as determined from integrations of the signals at δ = 5.79 ppm (major) and 5.86 ppm in the respective ^{1}H NMR spectra of the major and minor diastereomers in the crude reaction products. Catalytic hydrogenolysis of **6c** and **6d** removed the chiral auxiliary groups with concomitant removal of the benzyl-protecting groups to afford **6a** and **6b**, respectively, in 70% yields. Crystallization afforded both **6a** and **6b** in optically pure forms with $[\alpha]_D$ values of +9 and −9, respectively.

2.2. X-ray crystallography

In contrast to reports[17] that unprotected secondary amines in similar compounds are unstable, we were able to crystallize both enantiomers from benzene and obtain single-crystal X-ray structures and also determine their optical rotations. Figure 2 shows **6a** which, like compounds **2** and **4**, is both *S* and dextrorotatory. The X-ray structure revealed that a molecule of benzene is present in the crystal lattice.[18]

The single-crystal X-ray of **6b** had similar X-ray data[19] and as expected, it also contained a molecule of benzene in the crystal lattice.

3. Conclusions

Both enantiomers of the opium alkaloids, (*S*)- and (*R*)-*N*-norlaudanidine **6a** and **6b**, were synthesized in high enantioselectivity, respectively, using the chiral auxiliaries (*S*)- and (*R*)–α-methylbenzylamine in a Bischler–Napieralski cyclization. These free secondary amines could be isolated in high yields and for the first time afforded successful X-ray crystallographic structures and optical rotations.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.114.

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15. Yields in all the steps outlined in Scheme 1 were not optimized. Experimental details: ^{1}H NMR (500 MHz) and ^{13}C NMR (175 MHz) in $CDCl_3$ (unless otherwise noted).
Compound **10a:** To a stirred solution of oxalyl chloride (1.7 ml, 19.2 mmol) in anhydrous benzene (20 ml) were added 2,3-dimethoxyphenylacetic acid (3.2 g, 16 mmol) in one batch and DMF (1 drop). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride, which was used directly in the next

step. To a stirred mixture of (*S*)-α-methylbenzylamine (2.74 ml, 20.8 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 26.1 ml) was added dropwise a solution of the above-mentioned crude acid chloride in CH_2Cl_2 (30 ml) at 0 °C. After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was then evaporated. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford **10a** (4.4 g, 92%) as a colorless solid, mp 108–110 °C, ^{1}H NMR: δ 7.35–7.19 (m, 5H, Ar-H), 6.84–6.75 (m, 3H, Ar-H*), 5.65 (d, *J* = 10 Hz, 1H), 5.17–5.11 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.53 (s, 2H), 1.41 (d, *J* = 5 Hz, 3H); APCI-MS (*m*/*z*): 300.1 (M^++1, 100).

Compound **10b:** The preparation is as given for **10a** but with (*R*)-α-methylbenzylamine to afford **10b** (4.4 g, 92%) as a colorless solid, mp 108–110 °C.

Compound **11a:** To a solution of **10a** (2.1 g, 6.6 mmol) in anhydrous THF (60 ml) under Ar was added $BF_3{\cdot}Et_2O$ (0.41 ml, 3.2 mmol). The mixture was heated to gentle reflux and B_2H_6·THF (18 ml, 18 mmol) was then added dropwise. The reaction mixture was heated at reflux for 2 h, and then cooled to 0 °C and aqueous 20% HCl (100 ml) was added to the mixture. The reaction mixture which was stirred at 0 °C for 1 h and then overnight at rt was made basic to pH 13 with aqueous 50% KOH solution. The mixture was then extracted with CH_2Cl_2 (30 ml × 3). The combined organic layers were washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **11a** (1.7 g, 88%) as a viscous oil which was pure enough to be used directly in the next step without further purification. ^{1}H NMR: 7.31–7.20 (m, 5H, Ar-H), 6.78 (d, *J* = 10 Hz, 1H), 6.71 (dd, *J* = 10 & 2.5 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78–3.74 (q, *J* = 5 Hz, 1H), 2.76–2.67 (m, 4H), 1.52 (br, 1H), 1.32 (d, *J* = 10 Hz, 3H); ^{13}C NMR: δ 149.29, 147.81, 146.02, 133.04, 128.79, 127.26, 126.93, 121.00, 112.31, 111.68, 58.62, 56.33, 56.32, 49.33, 36.32, 24.71; MS (*m*/*z*): 284.2 (M^+, 22).Compound **11b:** The preparation is as given for **10a** but using **10b** to afford **11b** (1.6 g, 85%). ^{1}H and ^{13}C NMR spectra and APCI-MS data were identical with **11a**.

Compound **12a**: To a stirred solution of oxalyl chloride (1.0 ml, 11 mmol) in anhydrous benzene (20 ml) were added 3-benzyloxy-4-methoxyphenylacetic acid (derived in 3 steps[16] from **7**) (2.6 g, 9.6 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give acid chloride **8**, which was used directly in the next step. To a stirred mixture of **11a** (2.7 g, 9.6 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 12.8 ml) was added dropwise a solution of the crude acid chloride in CH_2Cl_2 at 0 °C. After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was then evaporated. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford **12a** (3.7 g, 72%) as a viscous oil whose NMR spectra were complex due to the presence of rotamers. APCI-MS (*m*/*z*): 540.3 (M^++1, 100).

Compound **12b**: The preparation is as given for **12a** but with **11b** to afford **12b** (3.7 g, 72%) as a colorless oil. APCI-MS (*m*/*z*): 540.3 (M^++1, 100).Compound **6c**: Compound **12a** (1.0 g, 1.8 mmol), $POCl_3$ (3.2 ml, 35 mmol), and benzene (50 ml) were combined under Ar and heated to reflux at 90 °C. After approximately 12 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 2 h. The resultant residue was redissolved in anhydrous MeOH (20 ml) and the solution was cooled to −78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.35 g, 9.2 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (10 ml), and the mixture was stirred at rt for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was basified by adding 20% KOH at 0 °C. Water and CH_2Cl_2 were added in the latter stage to solubilize the potassium salt and the amine. The mixture was extracted with CH_2Cl_2 (4 × 20 ml), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative-layer chromatography (30% EtOAc:hexane) to give compound **6c** (0.80 g, 75%) as a colorless oil. ^{1}H NMR: δ 7.39–7.13 (m, 10H, Ar-H), 6.73 (d, *J* = 5 Hz, 1H), 6.58 (s, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 6.46 (dd, *J* = 5 and 2.5 Hz, 1H), 5.79 (s, 1H), 5.00 (AB d, *J* = 13 Hz, 1H), 4.94 (AB d, *J* = 13 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (q, *J* = 8 Hz, 1H), 3.67 (t, *J* = 10 Hz, 1H), 3.48 (s, 3H), 3.26–3.14 (m, 2H), 3.01 (dd, *J* = 13 Hz and 2.5 Hz, 1H), 2.90–2.83 (m, 1H), 2.68–2.63 (m, 1H), 2.43 (dd, *J* = 10 and 2.5 Hz, 1H), 1.35 (d, *J* = 10 Hz, 3H); ^{13}C NMR: δ 148.34, 148.07, 147.56, 146.98, 146.58, 133.12, 129.96, 128.90, 128.60, 128.18, 127.79, 127.77, 126.98, 126.87, 123.05, 115.99, 111.85, 111.78, 111.57, 71.19, 61.13, 59.61, 56.60, 56.16, 55.90, 42.29, 40.23, 24.45, 23.79; 22.47. APCI-MS (*m*/*z*): 524.3 (M^++1, 100). $[\alpha]_D$ +20 (*c* 0.010, MeOH).

Compound **6d**: The preparation is as given for **6a** but with **6b** to afford **6d** (0.80 g, 75%) as a colorless oil. $[\alpha]_D$ −38 (*c* 0.010, MeOH). ^{1}H and ^{13}C NMR spectra and APCI-MS data were identical with **6c**.

Compound **6a**: To a solution of compound **6c** (200 mg, 0.38 mmol) in EtOAc (1.5 ml) and EtOH (4.5 ml) was added aqueous 10% HCl (0.83 ml). The resulting solution was hydrogenated over 10% Pd/C for 12 h with stirring. Filtration over Celite followed by evaporation of the solvent afforded a residue, which was dissolved in water (5 ml) and CH_2Cl_2 (5 ml), and basified to pH 13 with saturated $NaHCO_3$. The aqueous layer was then acidified to pH 7 and extracted with CH_2Cl_2 (3 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a brown oil which was purified by preparative TLC (silica gel, 30% EtOAc in hexane) to afford **6a** (90 mg, 72%) as a colorless solid, mp 140–141 °C (benzene). ^{1}H NMR: δ 6.83 (d, *J* = 2.5 Hz, 1H), 6.80 (d, *J* = 10 Hz, 1H), 6.71 (dd, *J* = 2.5 and 10 Hz, 1H), 6.62 (s, 1H), 6.59 (s, 1H), 4.17 (dd, *J* = 5 and 10 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.24–3.19 (m, 1H), 3.12 (d, *J* = 2.5 Hz, 1H), 3.10 (d, *J* = 5 Hz, 1H), 2.96–2.91 (m, 1H), 2.86–2.81 (m, 1H), 2.76–27.0 (m, 2H); ^{13}C NMR: δ 147.92, 147.46, 146.29, 145.90, 132.39, 130.56, 127.48, 121.19, 115.86, 112.21, 111.28, 109.88, 57.11, 56.37, 56.24, 42.30, 40.80, 29.62; APCI-MS (*m*/*z*): 330.1 (M^++1, 100). APCI-MS (*m*/*z*): 330.1 (M^++1, 100). $[\alpha]_D$ +9 (*c* 0.010, MeOH).

Compound **6b**: The preparation is as given for **6a** but with **6d** to afford **6b** as a colorless solid, (44 mg, 70%), mp 140–141 °C (benzene). ^{1}H and ^{13}C NMR spectra and APCI-MS were identical with **6a**. APCI-MS (*m*/*z*): 330.1 (M^++1, 100); $[\alpha]_D$ −9 (*c* .085, MeOH).

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18. X-ray crystallography of **6a** (from benzene): orthorhombic, *P*212121 (no. 19), *a* = 8.3887(17), *b* = 9.865(2), *c* = 26.407(6), *V* = 2185.3(8) Å^3, *Z* = 4, ρ_{calcd} = 1.238 g cm^{-3}, μ = 0.83 cm^{-1}, final R_1 = 0.0371 (for $I > 2\sigma I$), wR_2 = 0.0921 (for all data). The intensity data for **6a** and **6b** were recorded on a Rigaku AFC8-Saturn 70 system equipped with SHINE optic with MoKα radiation (*k* = 0.71070 Å) at 123(2) K. Compound **6a** was solved by direct methods and refined by full-matrix least-squares analysis on F^2 by using SHELXL. Hydrogen atoms were refined on the riding model with isotropic thermal parameters set twenty percent greater than those of their bonding partners. All other atoms were refined anisotropically.
19. X-ray crystallography of **6b**: Orthorhombic, $P2_12_12_1$ (no. 19), *a* = 8.389(2), *b* = 9.881(3), *c* = 26.420(7), *V* = 2190.0(11) Å^3, *Z* = 4, ρ_{calcd} = 1.236 g cm^{-3}, μ = 0.83 cm^{-1}, final R_1 = 0.0486 (for $I > 2\sigma I$), wR_2 = 0.1194 (for all data). The structure was solved by direct methods and refined by full-matrix least-squares analysis on F^2 by using SHELXL. Hydrogen atoms were refined on the riding model with isotropic thermal parameters set twenty percent greater than those of their bonding partners. All other atoms were refined anisotropically. CCDC 751551 and CCDC 740136 contain the supplementary crystallographic data. These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.