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# Relative and Absolute Stereocontrol in Intramolecular Nitrone Cycloadditions to the Cyclohexene Ring

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***Abstract***: The intramolecular reactivity of a nitrone derived from 2-(cyclohexen-3-yloxy)benzaldehyde has been investigated. By using (*R*)-α-phenylethylamine as chiral auxiliary, enantiomerically pure (9-amino-substituted) 1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ols were produced in satisfactory way.
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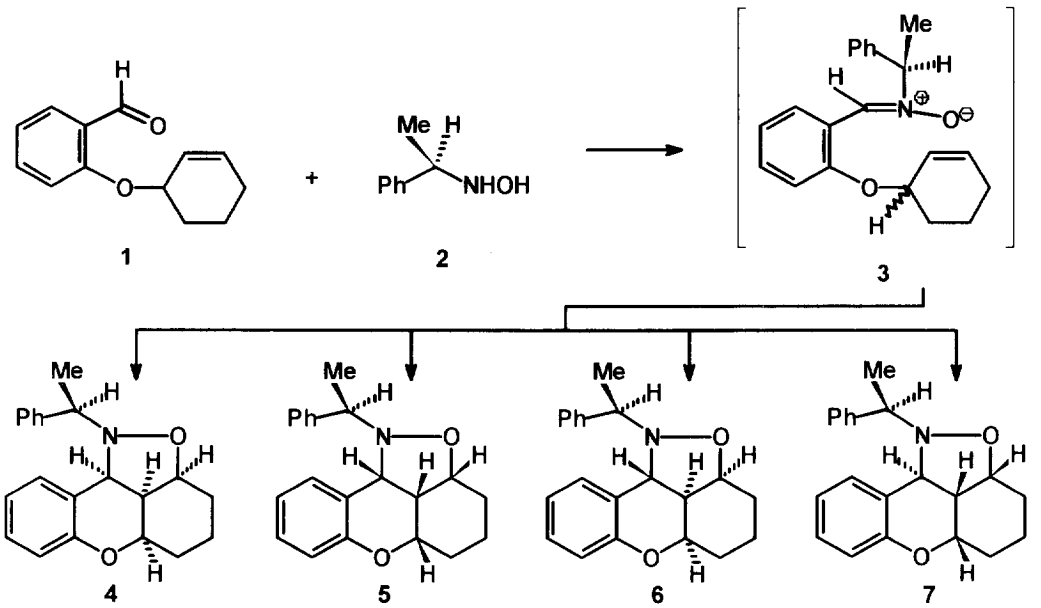
Intramolecular nitrone cycloadditions to alkenes represent a fruitful methodology for the synthesis of fused- and bridged-ring heterocycles as well as of polyfunctional open-chain molecules.[1-5] From the stereochemical point of view, this methodology may offer some advantages: (i) the concerted mechanism of the cycloaddition process warrants the retention of the alkene configuration; (ii) the geometric constraints due to the tether between the addends can dictate stereochemical preferences. In this context, we focused our attention on intramolecular cycloadditions to the cyclohexene ring by reasoning that the reduced rotational freedom of such moiety should favour the diastereofacial discrimination. The combination of this feature with the use of a homochiral nitrone functionality could then result in both relative and absolute stereocontrol. The present study is concerned with the behaviour of the readily accessible nitrone **3** and its potentiality in asymmetric syntheses (Scheme 1).

## Result and Discussion

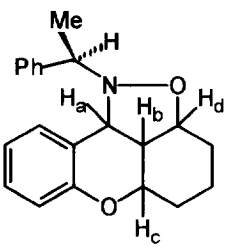
In order to generate the desired nitrone **3**, we treated 2-(cyclohexen-3-yloxy)benzaldehyde **1** with the homochiral hydroxylamine **2** in boiling toluene in the presence of anhydrous calcium chloride. Since isolation and characterisation of **3** seemed unnecessary, the reaction was prolonged until no further change was observed. The resulting product mixture, which counted for 90% of the starting organic material, contained four components, all of which were obtained in the pure state by column chromatography.




**Scheme 1.** Preparation of cycloadducts **4-7**

Analytical and spectral data were correct for diastereoisomeric cycloaddition products. Although the eight structures having a *trans* junction between the isoxazolidine and cyclohexane rings were rejected as being in contrast with the *Z* configuration of the dipolarophile, other eight diastereoisomeric structures remained conceivable. As the observed proton-proton coupling constants (Table 1) did not allow a clear-cut assignment of structure,[6-8] we submitted two of the four products to X-ray diffractometry study which demonstrated the structures **4** (Fig. 1) and **6** (Fig. 2).

**Table 1.** Proton-proton coupling constants of 1,2a,3,4,5,5a,10b,10c-octahydro-xantheno[9,1-*cd*]isoxazoles




| Compd. | $J_{ab}$ (Hz) | $J_{bc}$ (Hz) | $J_{bd}$ (Hz) |
|---|---|---|---|
| **4** | 8.9 | 4.0 | 7.2 |
| **5** | 8.9 | 4.4 | 8.1 |
| **6** | 11.9 | 6.9 or 7.1 | 6.9 or 7.1 |
| **7** | 12.0 | 6.6 or 6.9 | 6.6 or 6.9 |

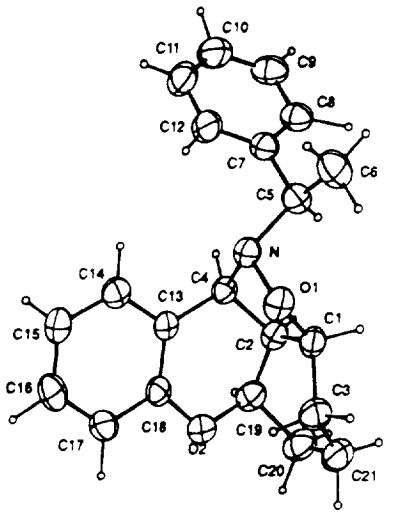



Figure 1. Molecular structure of 4

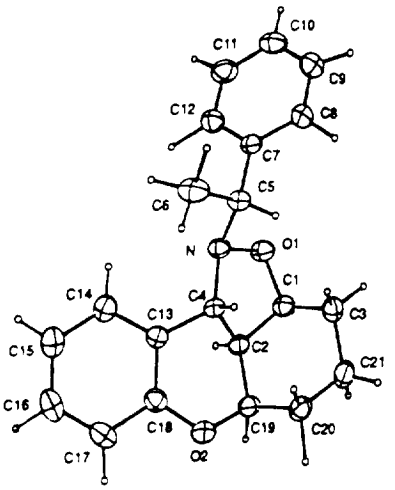
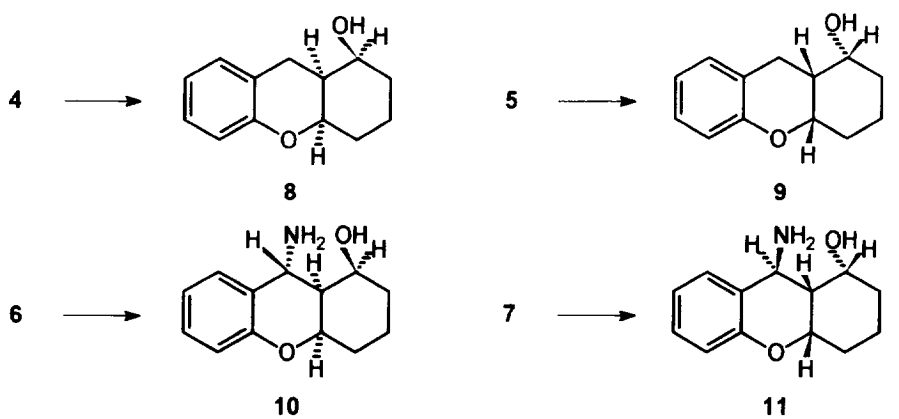



Figure 2. Molecular structure of 6

Hence we assigned the structures **5** and **7** on considering that the coupling constants between the hydrogens in the bridgehead positions are pratically the same (thus indicating the same relative stereochemistry) on going from **4** to **5** as well as on going from **6** to **7**. It is to be said that the $^1$H-NMR spectrum of the crude product mixture showed the following proportions: **4** = 55%, **5** = 35%, **6** = 5%, **7** = 5%.

The further stage of our work was the hydrogenolysis of the cycloadducts **4-7** in order to remove the chiral auxiliary linked to the nitrogen as well as to open the isoxazolidine ring so disclosing its masked functionalities.[3,9,10] Upon hydrogenation in acetic acid in the presence of Pd/C, compounds **4** and **5** gave the enantiomeric alcohols **8** and **9**, while compounds **6** and **7** gave the enantiomeric aminoalcohols **10** and **11** (Scheme 2).




**Scheme 2.** Hydrogenolysis of cycloadducts **4-7**

The above results reveal a highly stereoselective process. Indeed, no cycloadducts with a *trans* junction between the two hexatomic rings are formed because the dipole is constrained to attack the dipolarophilic face *syn* to the ethereal linkage. On the other hand, there is a massive predominance (90%) of the diastereoisomers having a fully *cis*-fused policyclic skeleton (formulae **4** and **5**). This outcome reflects a large preference for the less crowded *exo*-like approach by the *Z* nitrone configuration (Figure 3). The homochiral pendant happens to exert a little discrimination, which is not surprising due to the modest difference in steric encumbrance between hydrogen and methyl. Nevertheless, since both the resulting distereoisomeric cycloadducts are isolable in the pure state, the removal of the chiral auxiliary made available the final products in both enantiomeric forms. This certainly constitutes a valuable goal. It must be mentioned that a number of intramolecular nitrone cycloadditions to the cyclohexene ring have been previously reported;[7,11-16] however, to our knowledge, the only applications of this methodology to optically active targets are the syntheses of (+)-luciduline[17] and (-)-ptilocaulin.[18]

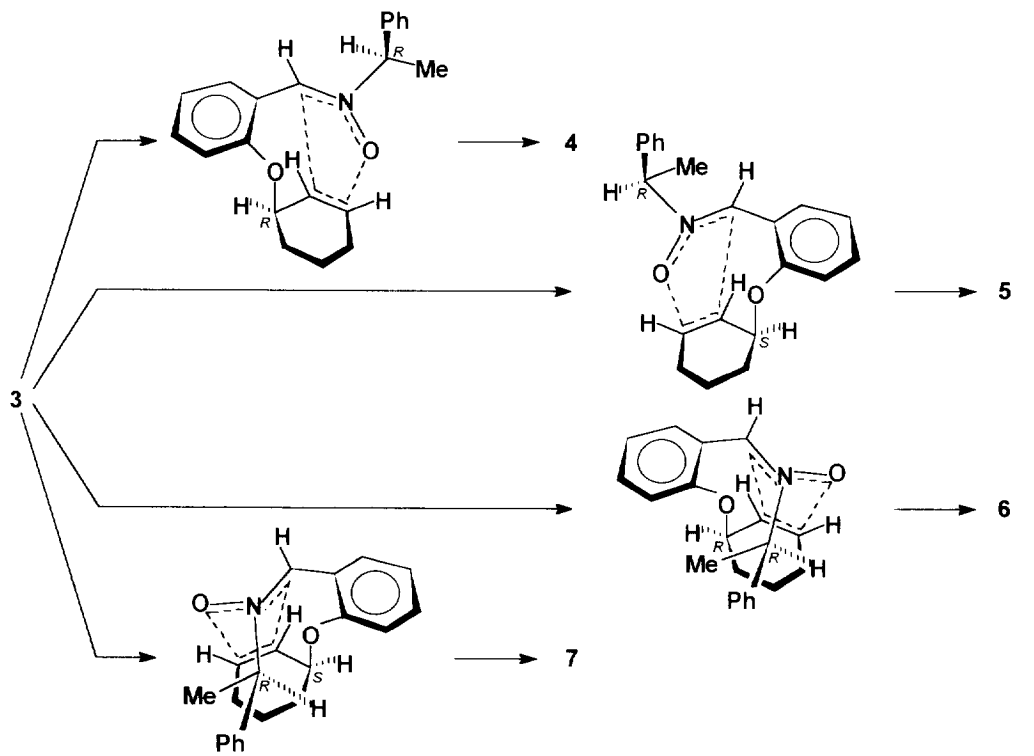



**Figure 3**. Transition states of the intramolecular cycloadditions

The difference in behaviour between **4**,**5** and **6**,**7** towards hydrogenolysis is surprising. A suggestive option is that the formation of **8**,**9** might involve *anti*-elimination of ammonia and subsequent stereoselective hydrogenation of the derived alkene.

## Experimental Section

M.p.s. were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin-Elmer 1725X spectrophotometer. $^1$H-NMR spectra were taken using a Bruker 300 MHz apparatus; chemical shifts are given in ppm from $SiMe_4$, with coupling constants in Hz. Mass spectra were determined with a VG-70EQ apparatus. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, with a 1 dm pathlength.

Compounds **1**[19] and **2**[20] were prepared according to literature methods.

**Reaction of aldehyde 1 with hydroxylamine 2.** Hydroxylamine **2** (1.4 g, 10.2 mmol) and anhydrous $CaCl_2$ (1.1 g, 10.2 mmol) were added to a solution of aldehyde **1** (1.7 g, 8.5 mmol) in toluene (300 ml). The mixture was heated at reflux for 48 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 5:1 as eluent. The first fractions gave (+)-(α*R*,2a*S*,5a*R*,10b*S*,10c*R*)-1,2a,3,4,5,5a,10b,10c-octahydro-1-(α-phenylethyl)xantheno[9,1-*cd*]isoxazole (**4**) (0.76 g, 28%). M.p. 119-120 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 1.48 (3H, d, *J*=6.4), 1.50-1.72 (2H, m), 1.82-2.05 (3H, m), 2.16-2.27 (1H, m), 2.88 (1H, ddd, *J*=4.0, 7.2, 8.9), 4.02 (1H, q, *J*=6.4), 4.10 (1H, ddd, *J*=1, 4.0, 7.9), 4.29 (1H, d, *J*=8.9), 4.46 (1H, ddd, *J*=6.0, 7.2, 8.0), 6.52 (1H, dd, *J*=1.7, 7.6), 6.71-6.77 (2H, m), 7.04 (1H, ddd, *J*=1.7, 7.7, 7.7), 7.28-7.46 (5H, m); $[\alpha]_D^{25}$ = +51 (c = 0.20 $CHCl_3$); MS: *m/z* = 321 ($M^+$); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2; N, 4.4. Found: C, 78.4; H, 7.0; N, 4.3. The next fractions contained (-)-(α*R*,2a*R*,5a*S*,10b*R*,10c*S*)-1,2a,3,4,5,5a,10b,10c-octahydro-1-(α-phenylethyl)xantheno[9,1-*cd*]isoxazole (**5**) (0.65 g, 24%). M.p. 134-135 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 1.34-1.94 (8H, overlapping), 2.10-2.22 (1H, m), 2.90 (1H, ddd, *J*=4.4, 8.1, 8.9), 4.03 (1H, q, *J*=6.3), 4.18-4.25 (2H, overlapping), 4.60 (1H, d, *J*=8.9), 6.80 (1H, d, *J*=8.1), 6.93 (1H, dd, *J*=7.3, 7.3), 7.12 (1H, ddd, *J*=1.5, 7.3, 7.3), 7.20-7.38 (6H, m); $[\alpha]_D^{25}$ = -31 (c = 0.20 $CHCl_3$); MS: *m/z* = 321 ($M^+$); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2; N, 4.4. Found: C, 78.6; H, 7.3; N, 4.2. Subsequent fractions contained (+)-(α*R*,2a*S*,5a*R*,10b*R*,10c*R*)-1,2a,3,4,5,5a,10b,10c-octahydro-1-(α-phenylethyl)xantheno[9,1-*cd*]isoxazole (**6**) (0.11 g, 4%). M.p. 174-175 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 0.51-0.60 (1H, m), 0.93-1.07 (1H, m), 1.23-1.36 (1H, m), 1.48-1.53 (1H, m), 1.62-1.68 (1H, m), 1.70 (3H, d, *J*=6.9), 2.03-2.07 (1H, m), 2.81 (1H, ddd, *J*=6.9, 7.1, 11.9), 3.82 (1H, d, *J*=11.9), 4.16 (1H, ddd, *J*=7.1, 7.1, 10.4), 4.30 (1H, q, *J*=6.9), 4.52 (1H, ddd, *J*=6.9, 6.9, 11.0), 6.90 (1H, d, *J*=8.1), 6.95 (1H, dd, *J*=7.5, 7.5), 7.19 (1H, dd, *J*=7.8, 7.8), 7.25-7.42 (6H, m); $[\alpha]_D^{25}$ = +295 (c = 0.20 $CHCl_3$); MS: *m/z* = 321 ($M^+$); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2; N, 4.4. Found: C, 78.7; H, 7.2; N, 4.3. Further elution gave (-)-(α*R*,2a*R*,5a*S*,10b*S*,10c*S*)-1,2a,3,4,5,5a,10b,10c-octahydro-1-(α-phenylethyl)xantheno[9,1-*cd*]isoxazole (**7**) (0.055 g, 2%). M.p. 149-150 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 0.77-0.90 (1H, m), 1.15-1.28 (1H, m), 1.42-1.70 (4H, overlapping), 1.74-1.83 (1H, m), 2.00-2.08 (1H, m), 2.15-2.26 (1H, m), 2.83 (1H, ddd, *J*=6.6, 6.9, 12.0), 4.15 (1H, d,

*J*=12.0), 4.27 (1H, ddd, *J*=6.9,7.2,10.2), 4.37 (1H, q, *J*=6.6), 4.58 (1H, ddd, *J*=6.6, 6.6, 11.1), 6.68-6.73 (2H, m), 6.83 (1H, d, *J*=8.1), 7.03-7.10 (1H, m), 7.22-7.39 (3H, m), 7.45-7.55 (2H, m); $[\alpha]_D^{25}$ = -46 (c = 0.07 $CHCl_3$); MS: *m/z* = 321 ($M^+$); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2; N, 4.4. Found: C, 78.4; H, 7.4; N, 4.5. On the basis of the $^1$H-NMR analysis, the above cycloadducts counted for 90% of the crude reaction mixture.

**Hydrogenation of 4.** A mixture of 10% Pd/C (90 mg) and **4** (234 mg, 0.73 mmol) in AcOH (10 ml) was stirred under $H_2$ for 6 h. After filtration through celite, the solvent was evaporated under reduced pressure to give (-)-(1*S*,4a*R*,9a*S*)-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol (**8**) (134 mg, 90%). M.p. 104-105 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 1.33-1.45 (1H, m), 1.63-1.91 (5H, m), 2.32-2.41 (1H, m), 2.76, 2.95 (2H, AB part of ABM system, $J_{AB}$=17.0, $J_{AM}$=7.2, $J_{BM}$=7.8), 3.95 (1H, ddd, *J*=4.6, 4.6, 9.2), 4.19 (1H, ddd, *J*=3.9, 3.9, 8.2), 6.78-6.84 (2H, m), 7.03-7.10 (2H, m); $[\alpha]_D^{25}$ = -26 (c = 0.20 $CHCl_3$); IR (nujol): 3250 $cm^{-1}$; MS: *m/z* = 204 ($M^+$); Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 76.3; H, 7.8.

**Hydrogenation of 5.** According to the procedure described in the preceding preparation, compound **5** (50 mg) gave (+)-(1*R*,4a*S*,9a*R*)-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol (**9**) (90 mg, 90%). Physical and spectroscopic data were the same as for **8**. $[\alpha]_D^{25}$ = +27 (c = 0.20 $CHCl_3$); Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 76.4; H, 7.7.

**Hydrogenation of 6.** A mixture of 10% Pd/C (50 mg) and **6** (136 mg, 0.42 mmol) in AcOH (6 ml) was stirred under $H_2$ for 6 h. After filtration through celite, the solvent was evaporated under reduced pressure. The residue was treated with NaOH 0.5N and extracted with $CH_2Cl_2$. The organic phase was separated, dried on $Na_2SO_4$ and evaporated to give (-)-(1*S*,4a*R*,9*R*,9a*S*)-9-amino-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol (**10**) (83 mg, 90%). M.p. 114-116 °C (hexane-benzene); $^1$H-NMR ($CDCl_3$) δ 1.24-1.93 (6H, m), 2.36 (1H, ddd, *J*=4.2, 4.2, 10.2), 3.89 (1H, ddd, *J*=4.2, 4.2, 10.8), 4.19 (1H, ddd, *J*=4.2, 4.2, 11.1), 4.25 (1H, d, *J*=10.2), 6.78 (1H, d, *J*=8.1), 6.92 (1H, dd, *J*=7.2, 7.2), 7.14 (1H, ddd, *J*=0.9, 7.2, 7.2), 7.24 (1H, d, *J*= 8.1); $[\alpha]_D^{25}$ = -52 (c = 0.35 $CHCl_3$); IR (nujol): 3270, 3360 $cm^{-1}$; MS: *m/z* = 219 ($M^+$); Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 8.0; N, 6.1.

**Hydrogenation of 7.** According to the procedure described in the preceding preparation, compound **7** (120 mg) gave (-)-(1*R*,4a*S*,9*S*,9a*R*)-9-amino-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol (**11**) (74 mg, 90%). Physical and spectroscopic data were the same as for **10**. $[\alpha]_D^{25}$ = +51 (c = 0.35 $CHCl_3$); Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.3; H, 7.8; N, 6.3.

**X-Ray diffraction analysis of 4 and 6.**[21] Unit cells parameters and intensity data were obtained on Enraf-Nonius CAD-4 diffractometer. Calculations were performed with the MolEN software[22] on a MicroVax-3100 computer. The cell dimensions were determined by least-squares fitting of 25 centered reflections monitored in

the range $30<\theta<35°$ for **4** and $33<\theta<38°$ for **6**. Correction for Lp and empirical absorption[23] were applied. Both the structures were solved by direct-methods (SIR88).[24] The non-hydrogen atoms were refined anisotropically by full-matrix least-squares. All the hydrogen atoms were found in the difference Fourier map, inserted with an overall isotropic atomic displacement parameter equal to 4.0 $Å^2$ and not refined. Atomic scattering factors were taken from ref. 25. Diagrams of the molecular structures were performed by ORTEP program[26] showing 30% probability displacement ellipsoids. Pertinent experimental details are given in Table 2.

**Table 2.** Crystal Structure Analysis: Experimental Details

| | **4** | **6** |
|---|---|---|
| Formula | $C_{21}H_{23}NO_2$ | $C_{21}H_{23}NO_2$ |
| MW | 341.42 | 341.42 |
| Crystal Size mm | 0.70×0.80×0.90 | 0.48×0.22×0.2 |
| Crystal Colour | colourless | pale yellow |
| System | orthorhombic | orthorhombic |
| Space Group | $P2_12_12_1$ | $P2_12_12_1$ |
| *a* Å | 9.487(1) | 6.401(1) |
| *b* Å | 10.390(2) | 11.875(1) |
| *c* Å | 17.369(6) | 22.527(2) |
| $\alpha, \beta, \gamma$ ° | 90 | 90 |
| V $Å^3$ | 1712(2) | 1712.3(2) |
| Z | 4 | 4 |
| Dcalc. Mg × $m^{-3}$ | 1.247 | 1.247 |
| Radiation | Cu $K_\alpha$ ($\lambda$ = 1.54184 Å) graphite monochromated | |
| μ $mm^{-1}$ | 0.592 | 0.592 |
| T K° | 293(3) | 293(3) |
| θ range ° | 2 - 70 | 2 - 70 |
| Scan Mode | ω - 2θ | ω - 2θ |
| Refls. Measured | $-11 < h < 11$ | $-7 < h < 7$ |
| | $0 < k < 12$ | $0 < k < 14$ |
| | $0 < l < 21$ | $0 < l < 27$ |
| Tot. Refls. Meas. | 3357 | 3420 |
| Unique Reflections | 1781 | 1881 |
| Rint | 0.014 | 0.013 |
| Obs. Refls. $[I > \sigma(I)]$ | 1763 | 1858 |
| R*; Rall | 0.063; 0.063 | 0.038; 0.039 |
| R** w=1 | 0.057 | 0.037 |
| Refined Parameters | 217 | 217 |

* $R = \Sigma||Fo|-|Fc|| / \Sigma|Fo|$; ** $Rw = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma w(Fo)^2]^{1/2}$

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