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Gentle Swelling of Pinan-6-One Derivatives

D. Hébrault and D. Uguen*

Laboratoire de Synthèse Organique, associé au CNRS
Ecole Européenne de Chimie, Polymères et Matériaux, Université Louis Pasteur
1, rue Blaise Pascal; 67008 Strasbourg (France)

A. De Cian and J. Fischer

Laboratoire de Cristallochimie, associé au CNRS
Université Louis Pasteur; 67070 Strasbourg (France)

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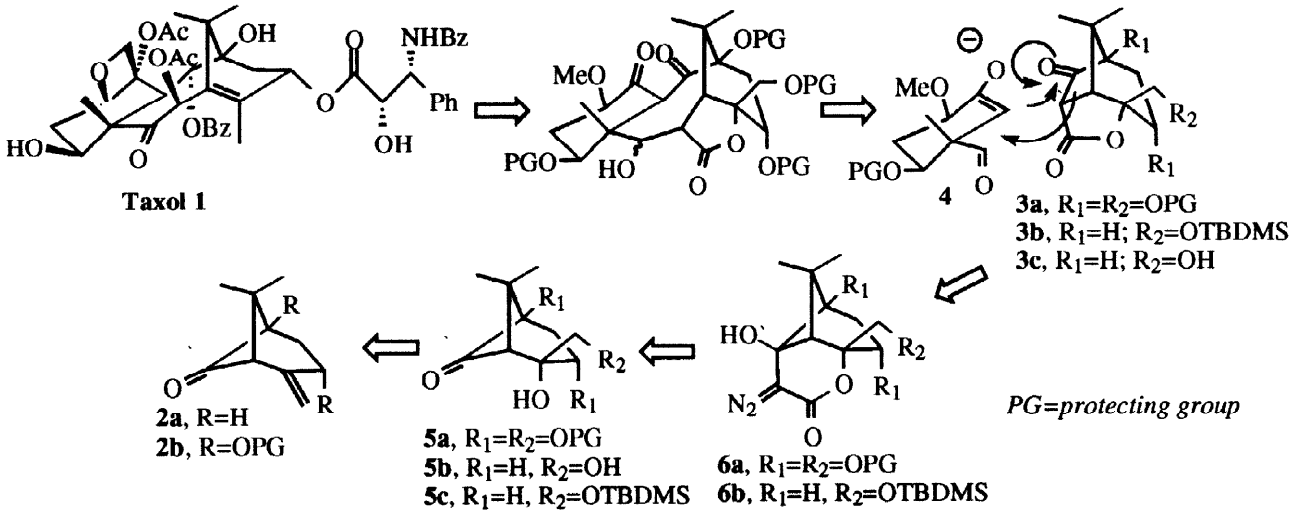
Abstract: The diazolactone **6b** rearranges by treatment with CF_3CO_2H to give the ketolactone **3b**, that, by sequential treatment with lithiated ethyl diazoacetate and AcOH, afforded the ketodiester **15**.

Due to the severe complexity of its structure, taxol **1** has long resisted to the efforts of synthetic chemists, the decisive onslaught being brought off by Nicolaou and Holton, who, independently, have achieved the first two total syntheses of taxol. Subsequently, various, equally effective, accesses to taxol have been reported, one of which, due to Wender, makes use of pinene as starting material.[1] As a continuation of our study of the reactivity of pinenone **2a**,[2] and inspired in some extent by Wender's approach to taxoids, we embarked on a synthesis of compound **1** by using the strategy outlined below.



Central in this plane is the recurrent use of a ring-enlargement process; first, to convert **5a** into the ketolactone **3a** *via* the diazo compound **6a**, next, to generate the taxol framework, the hope being that condensation of the lactone **3a** with the species **4** will result in a fragmentation, interception of the released enolate by the aldehyde residue giving the indicated bis-ketone. Obviously, it was safe to appraise the validity of this scheme by performing first model experiments with alleged substrates. The results of that exploratory studies are described in this Letter.

The possibility to enlarge a [3.1.1]bicycloheptanone into a [3.2.1]bicyclooctanone was verified by condensing the ketone **2a** with ethyl diazoacetate. Treatment of the resulting diazo compound **7** (62%) by HCl[3a] gave a mixture (56%) of the ketoesters **8a** and **9a** (Glc-mass, NMR), that smoothly decarboxylated by treatment with H_2O in DME[3d] to afford a 9/1 mixture (83%) of, respectively, the ketone **8b** and **9b**, as established by NMR. Since it can safely be assumed that ketone **8b** (res **9b**) originates from ketoester **8a** (res **9a**), it turns out that a one-carbon ring-expansion of ketone **2a** had taken place with preferential cleavage of the C-5/C-6 carbon carbon bond.

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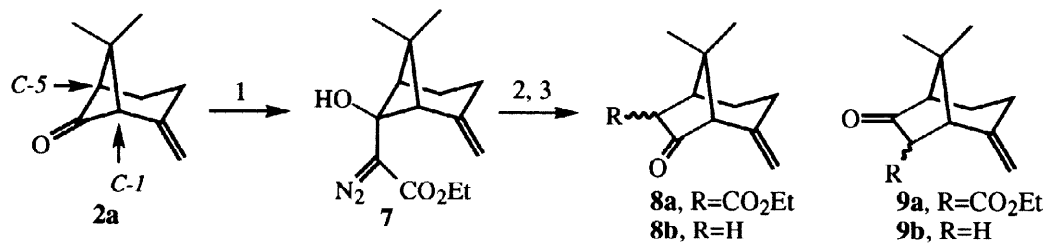
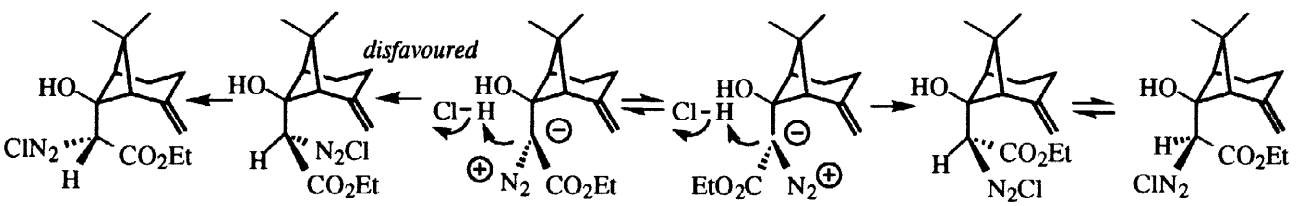
This observed selectivity merits comment. By analogy with a mechanism proposed in a related context,[3b] it may be inferred that slow protonation of compound **7** was followed by a fast semi-pinacol transposition of the resulting diazonium salts **10** and **11** to afford, respectively, the keto-esters **8a** and **9a**, effectively observed.[4] For steric reason, that protonation should occur, as indicated, at the front-side of the starting diazo molecule. In the event, of the two possible transition states, that leading to **11** should be disfavoured: the interaction of the ethoxycarbonyl group with the exo methylene residue that will rise, due to progressive hybridation change (from sp_2 to sp_3) of the carbon atom bearing the diazo group, will be more stringent than the corresponding interaction of the diazonium residue developped in the **7**-**10** conversion. Consequently, the kinetic product of that protonation should be the compound **10**, which, by a reduced rotation around the C-6/C-N_2 carbon carbon bond, corresponding to the least motion of the diazonium substituent, will progress to **10*i***, this conformational change being followed by a fast displacement of a nitrogen molecule by the antiperiplanar C-5 carbon atom to give the ketoester **8a**, indeed the main product.



2a **7**

Reagents and conditions: 1- 1M LDA (in THF; 3 eq.) added to a solution of **2a** and ethyl diazoacetate (2 eq.) in THF (3 ml/mmol); -78 °C to - 30 °C, 2 hours, then slow addition of AcOH (3 eq.), in THF (2 ml/mmol) (52%); 2- 1N aqueous HCl (1 eq.), THF (3.5 ml/mmol); 0 °C to r. t., 1.5 hours (56%); 3- H_2O (2 eq.), DME (4 ml/mmol); reflux, 18 hours (83%).



11*i* **11** **7** **7** **10** **10*i***

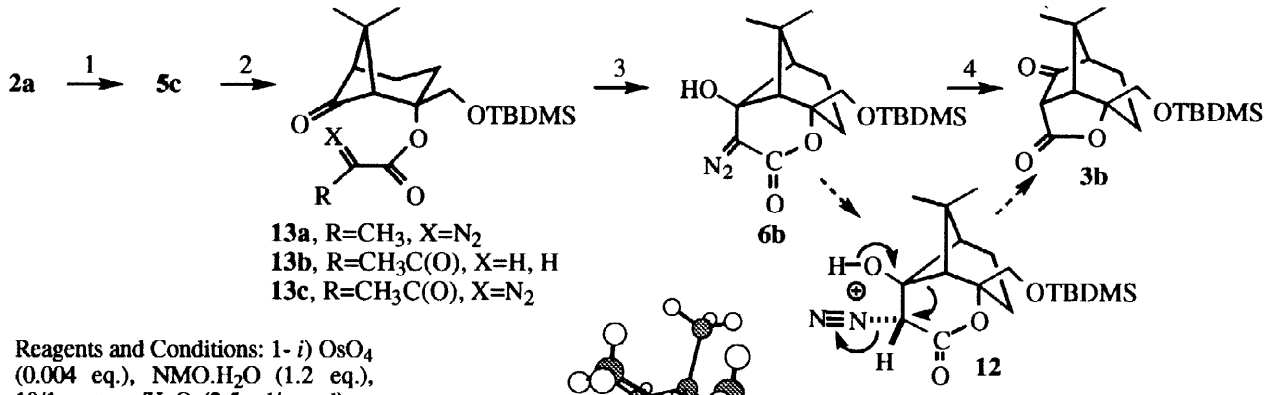
With regards to this mechanism, the related rearrangement of the model compound **6b** appeared promising: given the imposed location of the diazoester residue in **6b**, the protonation step should deliver a diazonium salt **12** ideally shaped (*vide infra*) for rearranging into the desired ketoester **3b**. This proved to be the case.

The diol **5b**, that formed in good yield by bis-hydroxylation of **2a** with the OsO_4/NMO system, was reacted with TBDMSCl to afford the monoprotected derivative **5c**. Initially, **5c** was converted into the corresponding diazoacetate **13a** by treatment with House's reagent.[5] Though this diazoester could be subsequently transformed into the diazo compound **6b** by treatment with LDA, the process was not really usefull due to the low yield registered in the esterification step (10%). A more efficient access was secured by condensing **5c** with diketene to form the acetoacetate **13b**. The ketoester **13b** was reacted with tosylazide and triethylamine to give the diazodiketone **13c**, that, by treatment with sodium methoxide, afforded the diazolactone **6b** (30 % overall, from **2a**).

This crystalline compound (M. p. 182-185 °C), whose structure could be determined by X-ray diffraction, decomposed sluggishly by treatment with HCl. However, slow addition of CF_3CO_2H to a solution of **6b** in CH_2Cl_2 resulted in the smooth formation of the lactone **3b**, as established by X-ray analysis, accompanied by its deprotected derivative **3c** (NMR). Treatment of this **3b**-**3c** mixture by TBDMSCl and imidazole afforded the pure lactone **3b** in excellent yield (91%). Additionnally, a kinetic experiment, performed in a NMR tube, showed that the rate of this rearrangement was roughly proportional to the acid concentration.

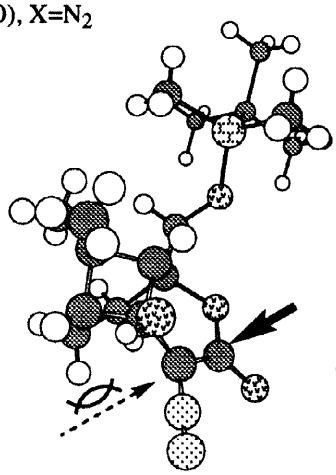
A rational for the selectivity of this rearrangement is as follows. As evidenced on the 3D-structure of **6b** generated from crystal data, owing to the interaction that would develop with the C-5 methylene group, inside

approach (dotted arrow) of the acid species perpendicularly to the plane formed by the diazoester residue should be disfavoured over the opposite approach (heavy arrow), in which case no hindrance will appear. Consequently, the salt **12** should form and instantly decompose to give the compound **3b**, effectively observed.

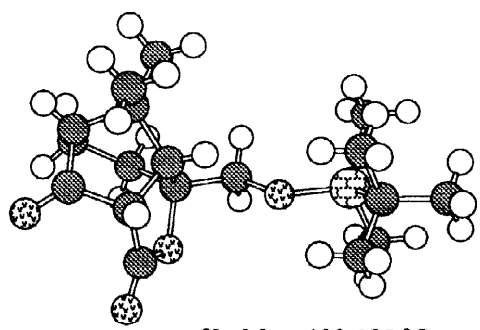


13a, R=CH_3, X=N_2
13b, R=$CH_3C(O)$, X=H, H
13c, R=$CH_3C(O)$, X=N_2

Reagents and Conditions: 1- *i*) OsO_4 (0.004 eq.), $NMO.H_2O$ (1.2 eq.), 10/1 acetone/H_2O (2.5 ml/mmol); r. t., 20 hours (58%); *ii*) TBDMSCl (1.5 eq.), imidazole (3 eq.), DMF (1.2 ml/mmol; r. t., 18 hours (97%); 2- *i*) diketene (1.5 eq.), DMAP (0.01 eq.), THF; 20-35 °C (exothermic!), 20 min. (88%); *ii*) Tosyl azide (1.5 eq.), NEt_3 (1.5 eq.), CH_3CN (1 ml/mmol); r. t., 1 hour (86%); 3- 0.1 M MeONa (in MeOH; 1 eq.); r. t., 1 hour (86%); 4- 5% CF_3CO_2H (in CH_2Cl_2, 30 ml/mmol); r. t., 3 hours, then conditions 1-*ii* (91%) or $RhCl(PPh_3)_3$ (0.005 eq.), toluene (3 ml/mmol); reflux, 4 hours (84%).



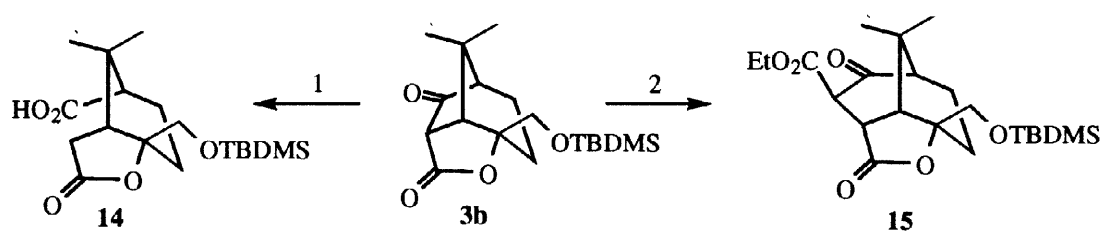
6b M. p. 182-185 °C



3b M. p. 103-105 °C

Attempted replacement of CF_3CO_2H by most of prevalent catalysts[3c] proved inefficient. However, treatment of **6b** by Wilkinson's catalyst in refluxing benzene afforded the lactone **3b** in high yield (84%).

Finally, the reactivity of compound **3b** was briefly examined. This lactone reacted smoothly with LiOH in THF to afford, after acidification, the acid **14** (86%). Additionnally, **3b** was condensed with lithiated ethyl diazoacetate, considered loosely as a model of the anion **4**, to give, after treatment of the crude reaction mixture by a solution of AcOH in THF, a single ketodiester (60%) to which the structure **15** was attributed by NMR.[6]



14 **3b** **15**

Reagents and conditions: 1- LiOH (3 eq.), THF (4 ml/mmol); r. t., 16 hours (86%); 2- *i*) LDA (3 eq.), ethyl diazoacetate (2 eq.), THF (7 ml/mmol); - 78 °C, 1 hour, then *in situ* addition of 0.25 M AcOH (in THF; 3eq.) (60%).

In conclusion, the results presented herein establish clearly the possibility to expand efficiently the cyclohexanone ring of 6-pinanone derivatives, which is an essential part of our planned synthesis of taxoids. Additionally, they shed some light on the Schollkopf diazo-ester ring-enlargement procedure,[3a] which can be viewed as occuring by slow, crucial on a stereochemical ground, protonation of the intervening hydroxy diazo compound, followed by a fast rearrangement of the resulting diazonium salt.

Acknowledgements: Thanks are due to Rhône-Poulenc Industrialisation for a grant (to D. H.).

References and Notes

1- Shibuya, S.; Isobe, M. *Synlett* **1998**, 373-374, and references cited therein.

2- Hébrault, D.; Uguen, D. preceding Letter. These results are taken in part from the thesis dissertation of D. H. (Strasbourg, 1995).

3- a) Schollkopf, U.; Bànhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann.* **1974**, 1767-1783; b) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459-465; c) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis*, **1983**, 197-199; d) Green, A. E.; Cruz, A.; Crabbé, P. *Tetrahedron Lett.* **1976**, *17*, 2707-2708.

4- A pathway involving a reversible protonation of **7** followed by preferential rearrangement of the diazonium salt **11** is unlikely: model examination of conformers **10*i*** and **11*i*** failed to reveal any significant energy difference.

5- House, H. O.; Blankley, C. J. *Organic Syntheses* **1969**, *49*, 22.

6- Selected data: **5b**: M. p. 74-75 °C; **5c**: C 64.44 (calc. 64.38), H 10.26 (calc. 10.13); ^{1}H NMR: 0.05 (s, 6H), 0.87 (s, 9H), 1.16 (s, 3H), 1.28 (s, 3H), 1.7 (t, J=7.7 Hz, 2H), 2.15-2.38 (m, 2H), 2.53-2.6 (m, 1H), 2.76 (d, J=7.3 Hz, 1H), 2.93 (s, 1H, O*H*), 3.38 (d (A part of an AB system), J_{AB}=9.7 Hz, Δν=46 Hz, 1H), 3.62 (d (B part of an AB system), J_{AB}=9.7 Hz, 1H); **7**: M. p. 84-86 °C; C 64.01 (calc. 63.61), H 7.61 (calc. 7.63), N 10.38 (calc. 10.6); ^{1}H NMR: 0.87 (s, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.62 (s, 3H), 1.83-1.95 (m, 2H), 2.33-2.43 (m, 3H), 2.79 (d, J=6.2 Hz, 1H), 2.9 (m, 1H, O*H*), 4.21 (q, J=7.1 Hz, 1H), 4.68 (d, J=1.7 Hz, 1H), 4.79 (dd, J=3.4, 1.7 Hz, 1H); **8b**: ^{1}H NMR: 0.94 (s, 3H), 0.97 (s, 3H), 1.43-1.55 (m, 1H), 1.82-2.19 (m, 5H), 2.45 (s, 1H), 2.56 (dd, J=19.2, 7.2 Hz, 1H), 4.6 (s, 1H), 4.69 (s, 1H); ^{13}C NMR: 21.9, 26.1, 26.8, 27.2, 40.5, 40.8, 41.6, 67.7, 110.3, 143.9, 218.5; **13a**: M. p. 78-80 °C; **13c**: M. p. 88-89 °C; **6b**: M. p. 182-185 °C; C 59.19 (calc. 58.99), H 8.22 (calc. 8.25), N 7.91 (calc. 7.64); ^{1}H NMR: 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.05 (s, 3H), 1.58-1.75 (m, 4H), 1.97-2.09 (m, 3H), 2.28-2.31 (m, 1H), 2.38 (d, J=6.2 Hz, 1H), 3.15 (s, 1H, O*H*), 3.61 (d (A part of an AB system), J_{AB}=11.3 Hz, Δν=15.3 Hz, 1H), 3.7 (d (B part of an AB system), J_{AB}=11.3 Hz, 1H); ^{13}C NMR: -5.1, 18.5, 24.6, 25.9, 26, 27.3, 28.8, 37, 49.4, 51.3, 61.1, 68.2, 74.9, 90.7, 167.8; **3b**: M. p. 103-105 °C; ^{1}H NMR: 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.01 (s, 3H), 1.22 (s, 3H), 1.6-2.25 (m, 5H), 2.99 (dd, J=7.3, 1.7 Hz, 1H), 3.35 (d, J=7.3 Hz, 1H), 3.59 (d (A part of an AB system), J_{AB}=11 Hz, Δν=27 Hz, 1H), 3.74 (d (B part of an AB system), J_{AB}=11 Hz, 1H); ^{13}C NMR: -5.32, -5.17, 18.5, 19.8, 21.4, 24.6, 26, 30, 36.8, 50.5, 53.6, 56, 68.4, 89.6, 168.6, 209.8; **3c**: M. p. 180 °C; **14**: M. p. 142-143 °C; C 60.89 (calc. 60.64), H 8.91 (calc. 9.05); ^{1}H NMR: 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.03 (s, 3H), 1.06 (s, 3H), 1.63-2.1 (m, 4H), 2.19-2.3 (m, 1H), 2.24 (dd, J=8.3, 3.2 Hz, 1H), 2.56 (d (A part of an ABX system), J_{AB}=17.9, 3.2 Hz, Δν=47 Hz, 1H), 2.81 (d (B part of an ABX system), J_{AB}=17.9, 8.5 Hz, 1H), 3.45 (d (A part of an AB system), J_{AB}=10.7 Hz, Δν=15 Hz, 1H), 3.74 (d (B part of an AB system), J_{AB}=10.7 Hz, 1H); ^{13}C NMR: -5.5, -5.4, 18.3, 19, 20.7, 25.9, 27.3, 29.7, 32.7, 34.5, 46, 53.3, 68,7, 89,4, 177.1, 180.1; **15**: ^{1}H NMR: 0.11 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.13 (s, 3H), 1.27 (t, J=7.2 Hz, 1H), 1.29 (s, 3H), 1.73-2.24 (m, 6H), 2.41 (dd, J=7.9, 2.2 Hz, 1H), 3.39 (d, J=2.2 Hz, 1H), 3.74 (d (A part of an AB system), J_{AB}=11.1 Hz, Δν=9.5 Hz, 1H), 3.81 (d (B part of an AB system), J_{AB}=11.1 Hz, 1H); 4.23 (q, J=7.2 Hz, 2H); ^{13}C NMR: -5.36, -5.21, 14.3, 18.5, 19.4, 22.4, 25, 25.8, 26, 29.2, 37.2, 52, 54.3, 60,9, 69, 88,8, 131,2, 163,1, 169,2, 208,8. ^{1}H and ^{13}C NMR at 200 and 50MHz, in $CDCl_3$. Crystal data for **3b** : $C_{18}H_{30}O_4Si$, M.W. = 338.5, orthorhombic, space group Pbca, a = 12.337(3), b = 14.410(4), c= 21.763(6) Å, U = 3868.9 Å^3, Z = 8, dcalc = 1.162 gcm^{-3}, m(MoKa) = 0.1318 mm^{-1}. Crystal data for **6b**: $C_{18}H_{30}N_2O_4Si$, M.W. = 366.5, orthorhombic, space group Pbca, a = 11.863(1), b = 12.745(1), c= 26.779(4) Å, U = 4048.8 Å^3, Z = 8, dcalc = 1.203 gcm^{-3}, m(MoKa) = 0.1332 mm^{-1}. Both data sets were collected at room temperature using graphite monochromated MoKa radiation (l = 0.7107 Å) on a Nonius-CAD4-F diffractometer. For **3b**, the crystal dimensions were 0.40*0.36*0.25 mm^3, 4389 data collected, 1835 with I > 3s(I). For **6b**, the crystal dimensions were 0.30*0.25*0.20 mm^3, 3997 data collected, 1597 with I > 3s(I). The structures were solved using direct methods and refined against |F| (full matrix, $s^2(F^2)$ = s^2_{counts} + 0.0064F^4). Hydrogen atoms were introduced as fixed contributors (C-H = 0.95 Å, B(H) = 1.3*Beqv of attached C). Final results : R(F)/Rw(F), GOF and deepest hole for **3b** = 0.044/0.065, 1.233, 0.20 eÅ^{-3}, for **6b** = 0.039/0.050, 1.081, 0.20 eÅ-3. For all computations, the Nonius OpenMoleN package on a DEC Alpha 3600S work station was used (OpenMoleN, Interactive Structure Solution, Nonius B.V., Delft, The Nederlands (1997)).