Stereoselective Synthesis of Azetidin-2-ones, Precursors of Biologically Active *syn*-3-Amino-2-hydroxybutanoic Acids

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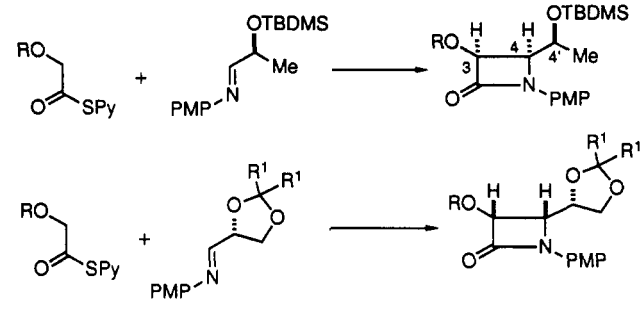
We recently reported[1] a simple, stereoselective one-pot synthesis of β-lactams by the reaction of the titanium enolates[2] of 2-pyridyl thioesters with chiral α-alkoxy and α,β-dialkoxy imines.[3] The imine diastereofacial selectivity is generally excellent, and 4,4′-syn configurated compounds are obtained in a highly stereocontrolled fashion. The reaction of *O*-benzyl or of *O*-acetyl (2-pyridylthio)glycolates[4] are particularly relevant, since 3,4-cis-4,4′-syn products are obtained in at least 96:4 diastereoisomeric ratios (Chart I).

In these products the *syn*-3-amino-2-hydroxy acid functionality is clearly embedded in a masked form. In light of the growing importance of this moiety in biologically active compounds, we decided to exploit our β-lactam synthesis as a convenient entry to some of these molecules.[5]

The synthesis of a precursor of the bestatin[6] component (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid was first attempted (Scheme I). From (S)-methyl mandelate was obtained imine (*S*)-1 in three steps, involving silylation with t-BuMe$_2$SiCl, DIBAL reduction, and reaction with benzylamine (63% overall yield). The crude imine was reacted with the titanium enolate of benzyloxy thioester **2** in CH_2Cl_2 at 0 °C for 5 h to afford, in 84% yield, compound **3** as a 94:6 mixture of 3,4-cis-4,4′-syn (**cs**) and 3,4-trans-4,4′-syn (**ts**) β-lactams,[7] as determined by comparison of their 300-MHz ^{1}H NMR spectra with those reported by Terashima et al.[5a,8] Flash chromatography

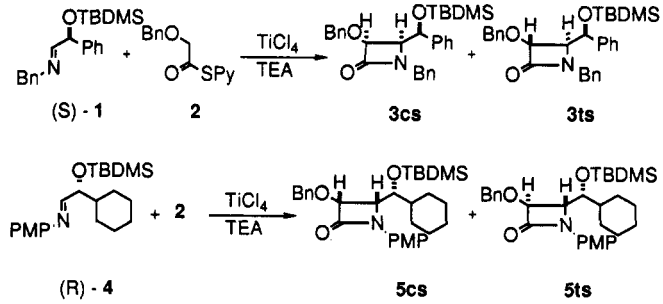
Chart I



R = $PhCH_2$, CH_3CO R^1 = Me, -$(CH_2)_5$-

Py = 2-Pyridyl TBDMS = *t*-BuMe$_2$Si PMP = 4-MeOPh

Scheme I



afforded pure **3cs**. This compound, obtained[5a] in 89:11 diastereoselectivity by Staudinger reaction of (benzyloxy)acetyl chloride and (*S*)-1, has already been converted into (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid by simple functional group manipulation.[5a]

The approach described in Scheme I was extended to the synthesis of a precursor of (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutanoic acid, the C-terminal residue of a renin inhibitor.[9] However, reaction of thioester **2** with imine (*R*)-**4**, prepared in 57% overall yield from (*R*)-methyl hexahydromandelate as described above, afforded a mixture of 3,4-cis-4,4′-syn and 3,4-trans-4,4′-syn β-lactams **5cs** and **5ts** in a disappointing 75:25 ratio (71% yield).[10] Moreover, several attempted deoxygenations of the hydroxy function at C-4′ failed.[11]

Therefore, an alternative route was designed (Scheme II). Condensation of thioester **2** with imines (*S*)-**6** or (*S*)-**7**, derived from (*R*)-cyclohexylideneglyceraldehyde, afforded compounds **8** (82% yield) and **9** (61% yield) in diastereoisomerically pure form after a single crystalli-

(1) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155.

(2) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Urpi', F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi', F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (d) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. For earlier references to this procedure for generating titanium enolates, see ref 2b,c.

(3) For other recent syntheses of β-lactams involving enolate condensation with chiral alkoxy imines see: (a) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984. (b) Andreoli, P.; Billi, L.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1991**, *47*, 9061. (c) Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933. (d) Fujisawa, T.; Ukai, Y.; Noro, T.; Date, K.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 7563. For reviews on the enolate imine condensation route to β-lactams see: (e) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (f) Brown, M. J. *Heterocycles* **1989**, *29*, 2225.

(4) The aldol condensation of the titanium enolates of α-alkoxy thioesters has been reported: Annunziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. *J. Org. Chem.* **1992**, *57*, 6339.

(5) For other β-lactam based approaches to 3-amino-2-hydroxy carboxylic acids see: (a) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (b) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737. (c) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayashinge, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (d) Georg, G. I.; Akgun, E.; Mashava, P. M.; Milstead, M.; Ping, H.; Wu, Z.-J.; Vander Velde, D. *Tetrahedron Lett.* **1992**, *33*, 2111. (e) Farina, V.; Hauck, S. I.; Walker, D. G. *Synlett* **1992**, 761. (f) Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068.

(6) (a) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263. (b) Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.* **1977**, *20*, 510.

(7) In these as in other β-lactams described in this work the cis/trans configuration of the azetidinone ring is easily determined by the HC-3/HC-4 coupling constant value (J_{cis} = 5.0–5.5 Hz; J_{trans} = 1.6–2.4 Hz).

(8) We did not find any evidence of the formation of the anti isomer of **3** by ^{1}H NMR analysis of the crude reaction mixture. When the reaction was repeated on the 4-methoxyphenyl analog of (*S*)-1, a slightly less unbalanced mixture of **cs** and **ts** isomers was obtained (90:10) in 60% yield.

(9) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707. For recent syntheses of this compound see ref 5a and: Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 360.

(10) The C-4/C-4′ syn configuration was tentatively assigned by analogy with the reaction of **2** with **1** and with other chiral α-[(*tert*-butyldimethylsilyl)oxy]substituted imines (see ref 1).

(11) Compound **5cs** was quantitatively desilylated to the alcohol (aqueous HF, acetonitrile, rt, 15 h) and transformed into the corresponding mesylate. The latter, however, did not undergo reduction in appreciable yields either with $LiBH_4$ in THF, with $NaBH_4$ in DMSO, or with NaI/Zn dust. Conversion of the alcohol into a thiocarbonyl derivative (for subsequent reduction with Bu_3SnH) occurred in very low yield.

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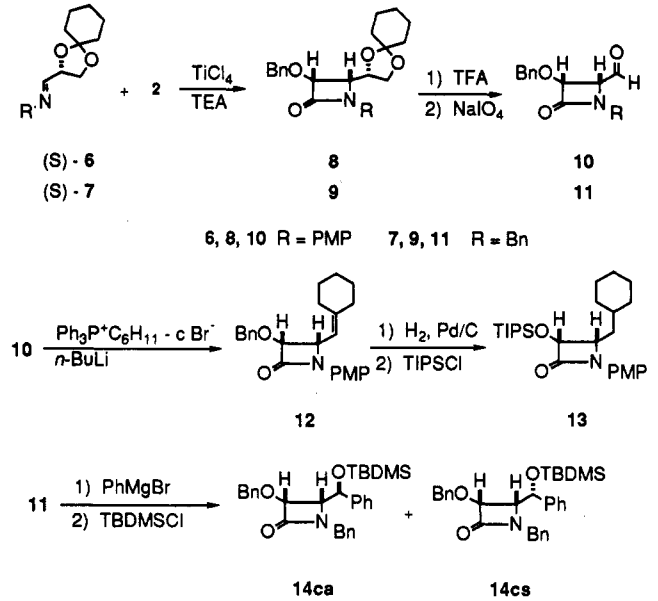
Scheme II



zation from hexane.[12] These were converted by hydrolysis and $NaIO_4$ oxidation into aldehydes (3*R*,4*R*)-**10** (80% overall yield)[13,14] and (3*R*,4*R*)-**11** (88% overall yield).[14,15] Wittig reaction of aldehyde **10** with the ylide derived from cyclohexyltriphenylphosphonium bromide gave alkene **12** (35–40% yield in different reaction conditions).[16] Finally, reaction with H_2 (1 atm) over 10% Pd/C reduced the double bond and removed the benzyl group to give the 3-hydroxy derivative (70% yield),[17] which was transformed into the TIPS ether **13** for correlative purpose. Compound **13** was identical by ^1H and ^{13}C NMR to that prepared and converted by Ojima et al.[5b,18] into (2*R*,3*S*)-3-amino-4-cyclohexyl-2-hydroxybutanoic acid.

Aldehydes as **10** and **11** can be useful starting material for the synthesis of the enantiomers of compounds related to **3**. For instance, PhMgBr addition to **11** (−30 °C) followed by silylation afforded (65% overall yield) an 82:18 mixture of 3,4-cis-4,4′-anti **14ta** and of 3,4-cis-4,4′-anti **14cs**, the enantiomer of **3cs**.[19] Remarkably, both these C-4′ epimeric products have been converted[5a] into the (2*R*,3*S*) C-terminal moiety of the above-mentioned renin inhibitor.

Experimental Section

(3*S*,4*S*)- and (3*R*,4*S*)-4-[(*S*)-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenylmethyl]-3-(phenylmethoxy)-1-(phenylmethyl)azetidin-2-ones (3cs and 3ts). To a stirred solution of thioester **2** (520 mg, 2 mmol) in CH_2Cl_2 (20 mL) cooled at −78 °C was added a 1 M CH_2Cl_2 solution of $TiCl_4$ (2 mL, 2 mmol) dropwise. After 5 min of stirring, triethylamine (0.280 mL, 2 mmol) was added dropwise, and the resulting purple solution was stirred at −78 °C for 30 min. Crude imine (*S*)-**1**[5a] (1 mmol) in CH_2Cl_2 was then added, and the mixture was stirred at 0 °C for 5 h. The reaction was quenched by addition of saturated $NaHCO_3$, and the mixture was filtered through Celite. The organic phase was separated, washed with water, dried, and concentrated. After NMR analysis, the crude product was purified by flash chromatography with a 50:50 hexanes/Et_2O mixture as eluant. Compound (3*S*,4*S*,4′*S*)-**3cs**, $[\alpha]^{22}_D$ +52.4 (*c* 0.8, $CHCl_3$), was obtained in 79% yield as an oil; compound (3*R*,4*S*,4′*S*)-**3ts** was obtained in 5% yield. These products had ^1H NMR spectra identical to those reported in the literature.[5a]

(3*S*,4*S*)- and (3*R*,4*S*)-4-[(*R*)-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexylmethyl]-1-(4-methoxyphenyl)-3-(phenylmethoxy)azetidin-2-ones (5cs and 5ts). Imine (*R*)-**4** was prepared from (*R*)-methyl α-hydroxycyclohexylacetate,[20] $[\alpha]^{22}_D$ −30.5 (*c* 2, $CHCl_3$) [lit.[20] $[\alpha]^{22}_D$ −31.3 (*c* 3, $CHCl_3$)] in three steps (see ref 5a) and was used as crude product. Condensation of this imine with thioester **2**, as described above for the synthesis of **3**, gave a 75:25 mixture of (3*S*,4*S*,4′*R*)-**5cs** and (3*R*,4*S*,4′*R*)-**5ts** in 71% yield. These products were separated by flash chromatography with a 50:50 hexanes/Et_2O mixture as eluant. **5cs**: oil; $[\alpha]^{22}_D$ +88.6 (*c* 3.5, $CHCl_3$); ^1H NMR (selected data) δ 4.65 (d, 1H, *J* = 5.5 Hz, HC-3), 4.25 (dd, 1H, *J* = 8.5, 5.5 Hz, HC-4), 4.10 (dd, 1H, *J* = 8.5, 3.5 Hz, HC-4′); IR 1745 cm^{-1}. Anal. Calcd for $C_{30}H_{43}NO_4Si$: C, 70.68; H, 8.50; N, 2.75. Found: C, 70.81; H, 8.42; N, 2.67. **5ts**: oil; $[\alpha]^{22}_D$ −9.0 (*c* 2, $CHCl_3$); ^1H NMR (selected data) δ 4.53 (d, 1H, *J* = 1.7 Hz, HC-3), 4.15 (dd, 1H, *J* = 1.7, 7.3 Hz, HC-4), 3.74 (dd, 1H, *J* = 4.3, 7.3 Hz, HC-4′).

(3*R*,4*S*)-4-(Cyclohexylmethylidene)-1-(4-methoxyphenyl)-3-(phenylmethoxy)azetidin-2-one 12. (A) Hydrolysis. Compound **8**[1,21] (507 mg, 1.2 mmol) was dissolved in 10 mL of a 50:50 mixture of CF_3COOH and water, and the solution was stirred overnight at rt. Solid $NaHCO_3$ was then cautiously added, and the mixture was extracted twice with CH_2Cl_2. The organic phase was dried, concentrated, and purified by flash chromatography with Et_2O as eluant to give the diol in yields ranging from 70 to 85% in different runs. The unreacted **8** was recovered and recycled. **(B) Oxidation.** To the diol (343 mg, 1 mmol) in ethyl acetate (10 mL) was added $NaIO_4$ (214 mg, 1 mmol) in water (3 mL), and the mixture was heated at 50 °C for 4 h. The cooled mixture was extracted twice with Et_2O, and the organic phase was dried and concentrated to give, in quantitative yield, the aldehyde **10**,[14] which was pure enough (by ^1H NMR) to be used without further purification. A sample of **10**, crystallized from ethyl acetate, had $[\alpha]^{22}_D$ +185.2 (*c* 1, CH_2Cl_2), mp 153 °C.[14] **(C) Olefination.** To a stirred solution of commercially available cyclohexyltriphenylphosphonium bromide (638 mg, 1.5 mmol) and n-BuLi (1.5 N in hexane, 1 mL) in THF (20 mL) cooled at −40 °C was added aldehyde **10** (313 mg, 1 mmol) in THF (10 mL) dropwise. The reaction was allowed to warm to rt and then stirred overnight. After addition of saturated NH_4Cl, the organic phase was separated, dried, and concentrated. The residue was purified by flash chromatography with a 60:40 hexanes/Et_2O mixture as eluant to give compound **12**: $[\alpha]^{22}_D$ −51.4 (*c* 0.6, $CHCl_3$); mp

(12) When we first reported the reaction of **2** with (*S*)-**6** we could detect only a single isomer of **7** by 300-MHz ^1H NMR. By carrying out the reaction on a 40 mmol scale, we were able to identify the minor component of the mixture as the trans/syn isomer of **8**.

(13) Unreacted **7** can be recovered from the crude product of the hydrolysis and recycled. The oxidation is quantitative and does not require chromatographic purification.

(14) (a) Palomo, C.; Cossio, F. P.; Cuevas, C. *Tetrahedron Lett.* **1991**, *32*, 3109. (b) Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360. Aldehyde **10**: $[\alpha]^{25}_D$ +179.2 (*c* 1, CH_2Cl_2), mp 152–153 °C. Aldehyde **11**: $[\alpha]^{25}_D$ +85.9 (*c* 1, CH_2Cl_2), mp 112–113 °C.

(15) These aldehydes can be useful intermediates also for the synthesis of β-hydroxyaspartic acid. For instance, aldehyde **10** was converted by $KMnO_4$ oxidation into the corresponding carboxylic acid. For a similar synthesis of this acid, and the subsequent transformation in a β-hydroxyaspartic acid derivative, see: Palomo, C.; Cabre', F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819.

(16) Different olefination procedures gave lower yields. In search for an alternative approach to the insertion of a cyclohexyl residue, aldehyde **10** was reduced ($NaBH_4$, 100% yield) to the alcohol, which was transformed into the corresponding tosylate. However, reaction of the latter with cyclohexyllithium/CuI did not afford the desired product.

(17) From the reduction a major byproduct was isolated (about 20% yield) which, on the basis of ^1H and ^{13}C NMR, is believed to be *N*-(4-methoxyphenyl)-4-cyclohexyl-3-hydroxybutanamide. Similar reduction yield was observed starting from the N-unprotected analog of **12**, obtained by CAN-promoted removal of the PMP group in 88% yield, performed following the procedure described by: Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

(18) We are indebted to Professor Iwao Ojima for providing us with the ^1H and ^{13}C NMR data of compound **13**.

(19) For a similar reaction see: Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429. The predominant formation of **14ca** is in agreement with Cram's model of stereoselection.

(20) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333.

(21) Compound **8** can also be prepared by the Staudinger reaction: Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307 and references cited therein.

64–66 °C; ^{1}H NMR (selected data) δ 5.34 (d, 1H, J = 9.5 Hz, =CH), 4.99 (dd, 1H, J = 4.8, 9.5 Hz, HC-4), 4.81 (d, 1H, J = 4.8 Hz, HC-3); IR 1750, 1580 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.44; H, 7.18; N, 3.75.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-1-(4-methoxyphenyl)-3-[[tris(1-methylethyl)silyl]oxy]azetidin-2-one (13) was obtained by reduction of compound **12** (113 mg, 0.3 mmol) with H_2 (1 atm) over 50 mg of 10% Pd on charcoal in THF (10 mL) for 15 h. The crude product was dissolved in DMF (1 mL), and imidazole (41 mg, 0.6 mmol) and TIPSCl (0.100 mL, 0.45 mmol) were added. The reaction was stirred at rt for 15 h. Et_2O was then added, and the mixture was washed with water. The organic phase was dried and concentrated, and the residue was purified by flash chromatography with a 70:30 hexanes/Et_2O mixture as eluant to give **13** in 60% overall yield from **12** as a low-melting material: ^{1}H NMR δ 6.85–7.30 (m, 4H, aromatic protons), 5.05 (d, 1H, J = 5.2 Hz, HC-3), 4.19–4.25 (m, 1H, HC-4), 3.80 (s, 3H, MeO), 0.85–2.00 (m, 34H); ^{13}C NMR δ 165.50, 156.06, 130.87, 118.53, 114.37, 76.19, 56.49, 55.48, 34.58, 34.27, 32.91, 26.51, 26.27, 26.17, 17.90, 17.82, 12.21; IR 1750 cm^{-1}.

(3*R*,4*R*,4′*S*)- and (3*R*,4*R*,4′*R*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenylmethyl]-3-(phenylmethoxy)-1-(phenylmethyl)azetidin-2-ones (14ca and 14cs). Aldehyde **11** was prepared from imine (*S*)-**7** and thioester **2** *via* β-lactam **9**, $[\alpha]^{22}_D$ +27.1 (*c* 1, $CHCl_3$), mp 91 °C, as described above for compound **10**. Aldehyde **11** had $[\alpha]^{22}_D$ +84.5 (*c* 1, CH_2Cl_2), mp 114–115 °C.[14] To a stirred solution of **11** (148 mg, 0.5 mmol) in THF (10 mL) cooled at −30 °C was slowly added a 0.3 M solution of PhMgBr in THF (2 mL, 0.6 mmol), and the mixture was stirred overnight at −30 °C. Saturated NH_4Cl was then added, the organic phase was separated, and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were dried and concentrated, and the crude product (70% yield) was treated with a 2-fold excess of TBDMSCl and imidazole in DMF (2 mL). After the workup described above for the sinthesis of **13**, the product was purified by flash chromatography with a 50:50 hexanes/Et_2O mixture as eluant to give compound **14ca**, $[\alpha]^{22}_D$ −17.0 (*c* 0.4, $CHCl_3$) in 53% yield, and **14cs**, $[\alpha]^{22}_D$ −50.8 (*c* 0.1, $CHCl_3$) in 12% yield, both as oils: ^{1}H NMR of compound **14ca** (selected data) δ 4.93 (dd, 1H, J = 5.0, 8.3 Hz, HC-4′), 4.65 (d, 1H, J = 5.0 Hz, HC-3), 3.67 (dd, 1H, J = 5.0, 8.3 Hz, HC-4); IR 1750 cm^{-1}. Anal. Calcd for $C_{30}H_{37}NO_3Si$ (**14ca**): C, 73.88; H, 7.65; N, 2.87. Found: C, 73.64; H, 7.77; N, 2.85. Found (**14cs**): C, 73.81; H, 7.60; N, 2.85.

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