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A Short Synthesis of (±)-Actinidine

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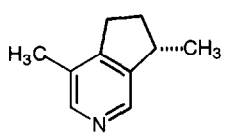
Abstract: The monoterpene alkaloid (±)-actinidine **10** is prepared in 5 steps from 3,4-dimethylpyridine using a pyridine radical cyclisation for the formation of the cyclopentano[c]pyridine skeleton.

The electron-deficient nature of the pyridine ring system makes the formation of carbon/carbon bonds to pyridine considerably more difficult than is the case for benzene as Friedel-Crafts chemistry is unavailable. At the 2- and 4-positions of pyridine, it is possible to form carbon/carbon bonds *via* nucleophilic substitution but the most common method for creating such bonds involves directed ortho-metallation.[1] Although aryl radicals have gained some prominence in recent years, the use of pyridine radicals in the formation of carbon/carbon bonds to the pyridine ring has been ignored almost completely. An early report demonstrated that nicotinyl peroxide can be decomposed in aromatic solvents to form 3-arylpyridines[2] whilst two more recent examples show that 2-bromopyridines can serve as radical precursors for the preparation of pyridinodihydrofurans[3] and pyridinothiophenes[4] respectively. We have recently utilised 3-bromopyridines in the synthesis of the alkaloid (±)-oxerine[5] and we now wish to present further results in this area leading to a concise synthesis of the monoterpene alkaloid (±)-actinidine.



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(-)-Actinidine **1** was first isolated from *Actinidia polygama* in 1959[6] and subsequently found in *Valeriana officinalis*.[7] It is a member of the relatively small class of monoterpene alkaloids so named owing to their biosynthetic origin. Interestingly, actinidine has also been found in insects; it has been identified in the defence secretion of the stick insect,[8] as the alarm pheromone in the ponorine ant[9] and in secretions of the rove beetle.[10] It also has an attractant effect on various mammals for example cats.[11] Recently, it has been shown to possess significant antifungal activity against *Macrophomina phaseolina*, a soybean pathogen.[12] There have been several syntheses of (±)-actinidine,[13] (+)-actinidine[14] and one synthesis of the natural enantiomer, (-)-actinidine **1**.[15] These syntheses clearly demonstrate the problems involved in creating carbon/carbon bonds on pyridine rings as with one exception, they all proceed from a suitable cyclopentane and build the pyridine ring onto this template. The alternative synthesis[13b] also builds the pyridine ring but by an intramolecular cycloaddition to a pyrimidine. As part of a project to explore the use of heteroaryl radicals in synthesis, we now report a synthesis of (±)-actinidine **10** using pyridine radical chemistry.

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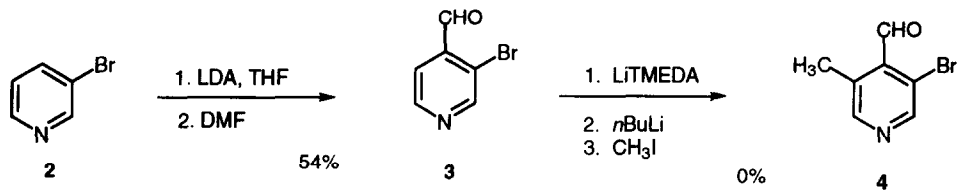


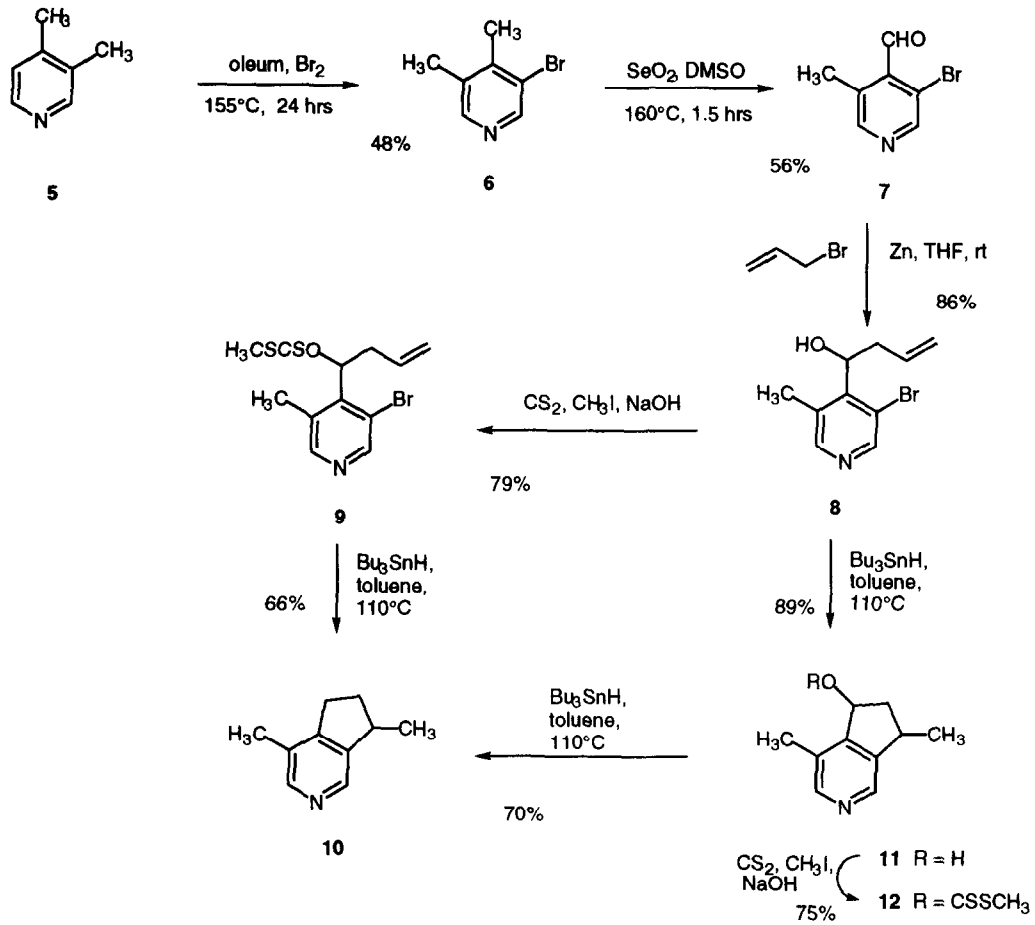
2 3 4

Scheme 1

The key intermediate in our synthesis is the trisubstituted pyridine, 3-bromo-4-formyl-5-methylpyridine **4**. Our initial attempts to prepare this compound are shown in scheme 1 and centred on ortho-lithiation chemistry. Thus, treatment of 3-bromopyridine **2** with lithium diisopropylamide (LDA) at -78°C followed by reaction with dimethylformamide (DMF) following the procedure of Corey[16] gave 3-bromo-4-formylpyridine **3** in 54% yield. Ortho-lithiation and methylation of **3** was explored using the addition of the lithium salt of N,N,N'-trimethylethylenediamine to the aldehyde followed by addition of *n*-BuLi to deprotonate at C-5.[17] Quenching the reaction with methyl iodide gave no trace of the desired product **4** across a wide range of temperatures and using several different bases. Subsequent experiments using 4-formylpyridine as the substrate for this reaction gave at best a 10% yield of the methylated product implying that a further activating group such as methoxy is needed on the pyridine ring.[17]

Consequently, we turned our attention to a route based on more classical pyridine chemistry starting from 3,4-lutidine **5** (scheme 2). Alkyl-substituted pyridines will undergo bromination under forcing conditions[18] and upon addition of bromine to a solution of **5** in oleum at 155°C a 48% yield of 3-bromo-4,5-dimethylpyridine **6** was obtained after purification by steam distillation and column chromatography. The role of SO_3 is clearly crucial as the reaction fails when carried out in concentrated sulfuric acid. Specific oxidation of the 4-methyl group was then achieved using SeO_2 in dimethylsulfoxide (DMSO)[19] at 160°C for 1 hr. Isolation and purification by chromatography, gave the desired 3-bromo-4-formyl-5-methylpyridine **7** as white needles in 56% yield. Although it was anticipated that this reaction would be regiospecific owing to the activation of methyl groups at the 2- and 4-position of pyridines, the structure of **7** was confirmed using nOe. Irradiation of the methyl group led to enhancements at the aldehyde proton and the proton attached to C-6.

With the required trisubstituted pyridine in hand, reaction using allylbromide and activated zinc under Barbier conditions in tetrahydrofuran (THF) gave in 86% yield the homoallylic alcohol **8**. At this point, two routes to actinidine are available. The first route involves formation of the xanthate (or other such radical leaving group)[20] followed by cyclisation and concomitant reduction. The second route involves radical cyclisation followed by xanthate formation and reduction. After some experimentation, reaction of **8** under phase transfer conditions[21] with NaOH solution, CS_2, CH_3I and catalytic Bu_4NHSO_4 gave xanthate **9** in 79% yield. Reaction of **9** under typical radical cyclisation conditions but using 3.5 equivalents of tributyltin hydride gave (±)-actinidine **10**, in 66% yield. The alternative pathway was also explored; treatment of **8** under radical cyclisation conditions gave **11** in 89% yield as a mixture of diastereomers (8:5). Although the assignment was not confirmed, previous work[5] and considerable literature precedent[22] indicates that the *cis*-isomer is the major product. Without separation of these diastereomers, reaction as previously gave the xanthates **12** in 75% yield and reaction with tributyltin hydride gave (±)-actinidine **10** in 70% yield. Although this second route is longer and slightly lower yielding, it has the potential to allow a synthesis of both enantiomers of actinidine in a stereodivergent manner. If the homoallylic alcohol **8** could be prepared in enantiomerically pure form by asymmetric allylation of the aldehyde **7** then cyclisation followed by separation of the diastereomers and hydroxyl group removal will lead to both enantiomers of actinidine.



Scheme 2

In summary, we have demonstrated the utility of radical chemistry in pyridines as a method for the creation of carbon/carbon bonds by carrying out a short synthesis of (±)-actinidine in (12%) overall yield.

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Experimental

General details

All reactions were carried out under argon and solutions dried with magnesium sulphate. Diethyl ether, tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl immediately before use. Acryloyl chloride and dimethyl sulphoxide were freshly distilled before use. Sodium hydride was washed with petrol or hexane at least 3 times before use. Column chromatography was performed with silica gel (Merck 7734) using the flash chromatography technique. Thin layer chromatographic analysis was performed using plastic-backed silica plates (Merck 5735). Components were visualised by either UV or phosphomolybdic acid dip. All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1605 FT-IR spectrophotometer. ^{1}H nmr spectra and ^{13}C NMR were

recorded on a Bruker AM360 spectrometer operating at 360 MHz for proton and 90 MHz for carbon. Tetramethylsilane (TMS) was adopted as the internal standard for ^{1}H nmr spectra and the solvent peaks for ^{13}C nmr spectra. Chemical shifts (δ_H and δ_C) are quoted as downfield from tetramethylsilane. The multiplicity of a ^{1}H nmr signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. High resolution mass spectra were performed at the Chemistry Department, King's College London. Elemental analysis of compounds was carried out at the Chemistry Department, University College London.

3-Bromo-4,5-dimethylpyridine (6)

3,4-Dimethylpyridine (5.13 ml, 46.6 mmol) was added slowly to fuming sulfuric acid (50 ml, 60% SO_3 in H_2SO_4) with vigorous stirring and cooling (ice bath). After complete dissolution, the solution was heated to 155°C and bromine (3 ml, 58 mmol) was added dropwise over 4 hours using a syringe pump. The reaction was heated at 155°C for 24 hours. After cooling to room temperature, the mixture was carefully poured into ice water and basified using NaOH solution. This mixture was then steam distilled and the distillate extracted with ether. The organic solution was dried and evaporated *in vacuo* to yield an oil which was purified by column chromatography (20% ethyl acetate in hexane). Pyridine **6** was isolated as white needles (4.2 g, 48%), m.p. 32-33°C (lit[18] m.p. 33-34°C); R_f (1:1 petrol:ethyl acetate) 0.53; δ_H(360 MHz; $CDCl_3$) 8.50 (1H, s, *pyr-H-2*), 8.22 (1H, s, *pyr-H-6*), 2.36 (3H, s, CH_3), 2.30 (3H, s, CH_3); δ_C ($CDCl_3$) 149.37, 148.63, 145.37, 133.80, 123.83, 18.90, 17.50; ν_{max} (NaCl)/cm^{-1} 1653 (C=C), 1558 (C=C); *m/z* 187/185 (100%, M^+), 106 (59%, M^+–Br), (Found: M^+, 184.9849. $C_7H_8{}^{79}BrN$ requires *M*, 184.9840).

3-Bromo-4-formyl-5-methylpyridine (7)

3-Bromo-4,5-dimethylpyridine **6** (0.5 g, 2.7 mmol) was dissolved in DMSO (5 ml) and the solution heated to 160°C. Selenium dioxide (295 mg, 2.7 mmol) was added slowly over 30 mins. After 1 hour a precipitate had appeared and the reaction was colled to room temperature. The mixture was filtered through a celite plug and poured into cold water (50 ml). This was extracted with diethyl ether (3 x 20 ml) and the organic solution dried and evaporated *in vacuo*. The resulting crude product was purified by flash chromatography (20% ethyl acetate in hexane) to give the pyridine aldehyde **7** (300 mg, 56%) as white needles, m.p. 72-73°C; R_f (1:1 petrol:ethyl acetate) 0.87; ν_{max}/cm^{-1} 1707 (C=O), 1653 (C=C), 1559 (C=C); δ_H (360 MHz; $CDCl_3$) 10.26 (1H, s, *CHO*), 8.71 (1H, s, *pyr-H-2*), 8.47 (1H, s, *pyr-H-6*), 2.36 (3H, s, CH_3); δ_C ($CDCl_3$) 193.32, 151.89, 151.24, 137.20, 134.90, 123.29, 17.38; *m/z* 201/199 (M^+, 100%), 170 (20%), 119 (25%), (Found: M^+, 198.9632 $C_7H_6NO^{79}Br$ requires *M*, 198.9633. Found: C, 42.34; H, 2.92; N, 6.78. C_7H_6NOBr requires C, 42.03; H, 3.02; N, 7.00).

3-Bromo-5-methyl-4-(but-3'-en-1'-ol)pyridine (8)

3-Bromo-4-formyl-5-methylpyridine **7** (120 mg, 0.6 mmol) was dissolved in THF (3 ml) and added dropwise under argon to a stirred mixture of allyl bromide (0.163 ml, 1.875 mmol) and activated zinc (195 mg, 3 mmol) in THF (5 ml) at room temperature. After 2 hours sodium hydrogen carbonate solution was added (10 ml, saturated) and the mixture was filtered through a celite plug. The resulting solution was extracted with diethyl ether (3 x 20 ml), the extracts dried, evaporated *in vacuo* and the crude product purified by flash chromatography (50% ethyl acetate in hexane) to give the desired pyridine **8** (126 mg, 86%) as a colourless oil; R_f (1:1 petrol:ethyl acetate) 0.4; ν_{max}/cm^{-1} 3297 (O-H), 1641 (C=C), 1560 (C=C); δ_H (360 MHz; $CDCl_3$) 8.38 (1H, s, *pyr-H-2*), 8.14 (1H, s, *pyr-H-6*), 5.83-5.72 (1H, m, *CH*=CH2), 5.22 (1H, t, *J* 7, *CHOH*), 5.13-5.07 (2H, m, CH=CH_2), 2.99 (1H, s, *OH*), 2.55 (1H, dt, *J* 14, 6, OCHCH_2), 2.48 (1H, dt, *J* 14, 6, OCHCH_2) 2.41 (3H, s, pyr-CH_3); δ_C ($CDCl_3$) 151.44, 150.53, 148.20, 134.23, 134.00, 121.30, 119.20, 73.10, 39.88, 18.00; (Found: M^+, 241.0107 $C_{10}H_{12}NO^{79}Br$ requires *M*, 241.0102).

3-Bromo-5-methyl-4-(but-3'-en-1'-ol)pyridine xanthate (9)

A solution of alcohol **8** (125 mg, 0.52 mmol) and methyl iodide (0.075 ml, 0.57 mmol) was added to a two-phase system consisting of CS_2 (1.13 ml) and aqueous sodium hydoxide (1.5 ml, 50% w/v) containing nBu_4NHSO_4 (17 mg, 0.05 mmol) and stirred for 1 hr at room temperature. The reaction mixture was extracted with dichloromethane (3 x 20 ml), the organic extracts were dried and evaporated *in vacuo* and the crude product was purified by flash chromatography (20% ethyl acetate in hexane) to give the xanthate **9** (137 mg, 79%) as a colourless oil. R_f (50% ethyl acetate in hexane) 0.71; ν_{max}/cm^{-1} 1643 (C=C), 1206 (C=S); δ_H (360 MHz; $CDCl_3$) 8.48 (1H, s, *pyr-H-2*), 8.20 (1H, s, *pyr-H-6*), 6.63 (1H, dd, *J* 8, 5.4, C*H*OC), 5.83-5.71 (1H, m, C*H*=CH2), 5.13 (1H, dt, *J* 15.4, 1.5, CH=C*Hcis*H), 5.09 (1H, dt, *J* 8.7, 1.5, CH=C*Htrans*H), 2.91 (1H, dt, *J* 14.6, 8, OCHCH_2), 2.64 (1H, m, OCHCH_2) 2.51 (3H, s, SC*H*3), 2.38 (3H, s, pyr-CH_3); δ_C ($CDCl_3$) 214.02, 150.98, 150.72, 143.81, 133.16, 132.02, 119.16, 117.52, 82.36, 36.83, 19.47, 17.63; *m/z* 333/331 (M^+, 55%), 252 (70%), 226/224 (70%), 144 (100%), (Found: M^+, 330.9769 $C_{12}H_{14}NO^{79}BrS_2$ requires *M*, 330.9700).

(±)-Actinidine (10) via *in situ* reduction/cyclisation

A solution of the xanthate **9** (60 mg, 0.18 mmol) and tributyltin hydride (0.15 ml, 0.60 mmol) were heated in toluene (7 ml) at 110°C under argon and AIBN (*ca.*5 mg) was added. The reaction was stirred at 110°C for 2 hr. After cooling, the reaction mixture was poured into water (20 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were washed with aqueous ammonia (0.88, 3 x 20 ml) and the organic solution was dried and evaporated *in vacuo*. Purification by flash chromatography (50% ethyl acetate in hexane) gave (±)-actinidine **10** as a colourless oil (17.6 mg, 66%); R_f (50% ethyl acetate in hexane) 0.18; δ_H (360 MHz; $CDCl_3$) 8.26 (1H, s, *pyr-H-6*), 8.19 (1H, s, *pyr-H-2*), 3.27 (1H, sext., *J* 7, C*H*CH_3), 2.91-2.83 (1H, ddd, *J* 17, 9, 4, pyr-CH_2), 2.78-2.69 (1H, dt, *J* 17, 8.4, pyr-CH_2), 2.39-2.28 (1H, m, CH_2), 2.24 (3H, s, pyr-CH_3) 1.68-1.57 (1H, m, CH_2), 1.31 (3H, d, *J* 7, CH_3); δ_C ($CDCl_3$) 152.01 (C), 147.69 (CH), 142.56 (CH), 137.14 (C), 129.14 (C), 37.95 (CH), 33.84 (CH_2), 29.74 (CH_2), 20.08 (CH_3), 16.03 (CH_3); *m/z* 147 (M^+, 80%), 132 (100%), 117 (32%), 69 (28%), (Found: M^+, 147.1052 $C_{10}H_{13}N$ requires *M*, 147.1048).

4,7-Dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridin-5-ol (11)

The alcohol **8** (120 mg, 0.49 mmol) and Bu_3SnH (0.31 ml, 1.23 mmol) were dissolved in toluene (10 ml) and heated to 110°C under reflux conditions under an argon atmosphere. Azo-bis(isobutyronitrile) (AIBN, *ca.* 5 mg) was added and the reaction stirred at 110°C for 2 hours. After cooling, the reaction mixture was poured into water (20 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were washed with aqueous ammonia (0.88, 3 x 20 ml) and the organic solution was dried and evaporated *in vacuo*. Purification by flash chromatography (67% ethyl acetate in hexane) gave the product **11** (70.8 mg, 89%) as an 8:5 mixture of diastereomers; R_f (50% ethyl acetate in hexane) 0.13; ν_{max}/cm^{-1} 3364 (O-H), 1594 (C=C); **major, *cis*-isomer** δ_H (360 MHz; $CDCl_3$) , 8.21 (1H, s, pyr-*H*), 8.16 (1H, s, pyr-*H*), 5.30-5.24 (1H, m, C*H*OH), 3.51-3.45 (1H, sextet, *J* 7, C*H*CH_3), 2.40 (3H, s, pyr-CH_3), 2.33-2.27 (1H, m, CH_2), 1.62-1.54 (1H, m, CH_2), 1.36 (3H, d, *J* 7, CHCH_3); δ_C ($CDCl_3$) 151.24, 148.48, 143.05, 142.65, 130.39, 74.38, 44.73, 35.39, 21.03, 15.29; **minor, *trans*-isomer** δ_H (360 MHz; $CDCl_3$) , 8.21 (1H, s, pyr-*H*), 8.13 (1H, s, pyr-*H*), 5.30-5.24 (1H, m, C*H*OH), 3.11-3.05 (1H, sextet, *J* 7, C*H*CH_3), 2.78-2.70 (1H, m, CH_2), 2.37 (3H, s, pyr-CH_3), 1.93-1.85 (1H, m, CH_2), 1.28 (3H, d, *J* 7, CHCH_3); δ_C ($CDCl_3$) 151.24, 148.65, 143.16, 143.44, 130.05, 73.24, 44.46, 35.09, 19.90, 15.26; *m/z* 163 (M^+, 100%), 148 (M^+- CH_3, 58%), 145 (M^+-H_2O,57%), (Found: M^+, 163.0995 $C_{10}H_{13}NO$ requires *M*, 163.0997).

(±)-Actinidine (10) via the xanthate ester of 4,7-Dimethyl-6,7-dihydro-5H-cyclopenta[c]-pyridin-5-ol (11) and reduction

A solution of alcohol **11** (60 mg, 0.36 mmol) and methyl iodide (0.025 ml, 0.39 mmol) was added to a two-phase system consisting of CS_2 (0.36 ml, 6.02 mmol) and aqueous sodium hydoxide (0.42 ml, 50% w/v)

containing nBu_4NHSO_4 (14 mg, 0.036 mmol) and stirred for 1 hr at room temperature. The reaction mixture was extracted with dichloromethane (3 x 20 ml), the organic extracts were dried and evaporated *in vacuo* and the crude product was purified by flash chromatography (25% ethyl acetate in hexane) to give the xanthates **12** (72 mg, 75%) as mixture of diastereomers in a ratio of 8:5. R_f (50% ethyl acetate in hexane) 0.26; ν_{max}/cm^{-1} 1640 (C=C), 1210 (C=S); **major, *cis*-isomer** δ_H (360 MHz; $CDCl_3$) 8.43 (1H, s, pyr-*H*), 8.34 (1H, s, pyr-*H*), 7.00-6.95 (1H, overlapping m, C*H*OCSSMe), 3.57-3.51 (1H, sextet, *J* 7, C*H*CH_3), 2.56 (3H, s, pyr-C*H*$_3$), 2.55-2.48 (1H, m, C*H*$_2$), 2.29 (3H, s, SC*H*$_3$), 2.18-2.04 (1H, m, C*H*$_2$), 1.36 (3H, d, *J* 7, CHC*H*$_3$); δ_C ($CDCl_3$) 210.57, 148.92, 146.33, 144.93, 143.72, 130.85, 84.57, 40.74, 35.93, 19.97, 19.31, 15.57; **minor, *trans*-isomer** δ_H (360 MHz; $CDCl_3$) 8.43 (1H, s, pyr-*H*), 8.32 (1H, s, pyr-*H*), 7.00-6.95 (1H, overlapping m, C*H*OCSSMe), 3.31-3.25 (1H, sextet, *J* 7, C*H*CH_3), 2.98-2.90 (1H, m, C*H*$_2$), 2.58 (3H, s, pyr-C*H*$_3$), 2.28 (3H, s, SC*H*$_3$), 1.87-1.74 (1H, m, C*H*$_2$), 1.39 (3H, d, *J* 7, CHC*H*$_3$); δ_C ($CDCl_3$) 210.57, 148.92, 146.33, 144.93, 143.89, 130.85, 84.57, 40.74, 35.81, 21.71, 19.31, 15.50. The xanthates **12** (20 mg, 0.06 mmol) and Bu_3SnH (0.03 ml, 0.15 mmol) were dissolved in toluene (2 ml) and heated to 110°C under reflux conditions under an argon atmosphere. AIBN (*ca.* 3 mg) was added and the reaction stirred at 110°C for 2 hours. The toluene was evaporated *in vacuo* and the residue was purified by flash chromatography (hexane followed by 50% ethyl acetate in hexane) to give (±)-actinidine **10** as a colourless oil (11.2 mg, 70%) identical in all respects to the previous sample.

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