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Synthesis of (−)-pinidinone

Kristína Csatayová [a], Ivan Špánik [b], Veronika Ďurišová [a], Peter Szolcsányi [a,*]

[a] Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia
[b] Department of Analytical Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

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ABSTRACT

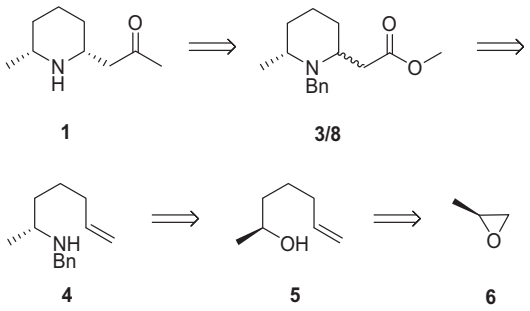
The diastereoselective $PdCl_2/CuCl_2$-catalysed intramolecular methoxyaminocarbonylation of *N*-benzyl protected alkenyl amine **4** was used as a key step in the total synthesis of the naturally occurring piperidine alkaloid (−)-pinidinone. Commercially available (*S*)-propylene oxide was employed as starting material, delivering the key substrate **4** in three steps and 68% overall yield. Subsequently, the influence of various reaction parameters on the diastereoselectivity of the key cyclisation of **4** was scrutinised. Copper(II) chloride proved to be the optimum reagent and/or co-catalyst for the successful aminocyclisation-methoxycarbonylation tandem transformation of alkenyl amine **4** into the desired methyl esters **3** and **8**. The latter were subsequently transformed into the title natural product.

(−)-Pinidinone [(2*R*,6*R*)-1-(6-methyl-piperidin-2-yl)-propan-2-one] (**1**) (Scheme 1) is a naturally occurring alkaloid isolated[1a] from the needles of the Colorado blue spruce (*Picea pungens* Engelm.) and its biosynthesis has been proposed.[1b] It was also found in the hemolymph of the Australian mealybug ladybird[1c] (*Cryptolaemus montrouzieri* Mulsant) as well as the Mexican bean beetle[1d] (*Epilachna varivestis* Mulsant). It is thought that (−)-pinidinone (**1**) serves as an antifeedant and/or defensive alkaloid against worms (spruce) and/or ants and spiders (beetles). To the best of our knowledge, there are only two non-racemic[1a,2] total syntheses of **1** to date.

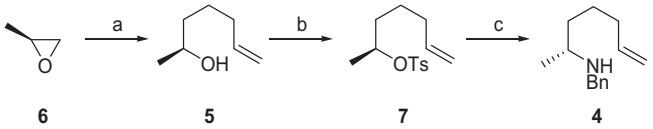
In the frame of our research programme aimed at the application of novel palladium-catalysed aminocyclisations in the total synthesis of alkaloids,[3] we decided to apply Pd(II)-catalysed methoxyaminocarbonylation[4] as the key step in the synthesis of **1**. Our retrosynthetic analysis led, via the corresponding esters **3** and/or **8**, to the alkenyl amine **4** as a key substrate. This olefin could be prepared from the secondary alcohol **5** which, in turn, is obtained from commercially available (*S*)-propylene oxide (**6**) (Scheme 1).

The synthesis of **1** began from the enantiomerically pure epoxide **6** which underwent highly regioselective ring-opening[5] with butenylmagnesium bromide in the presence of a catalytic amount of freshly prepared Li_2CuCl_4 to furnish (2*S*)-hept-6-en-2-ol (**5**) in 88% yield. Activation[6] of the hydroxy group followed by treatment of the resulting crude tosylate **7** with excess benzylamine gave, in 77% yield, the desired (*R*)-*N*-benzyl-(1-methyl-hex-5-enyl) amine (**4**) over two steps (Scheme 2).

With the desired substrate **4** in hand, it was first subjected to the Pd(II)-catalysed methoxyaminocarbonylation under standard catalytic conditions in anhydrous MeOH. We obtained a diastereomeric mixture of easily separable piperidines **3** and **8** in the ratio 83/17 in 58% combined isolated yield (Scheme 3).



Scheme 1. Retrosynthetic analysis of (−)-pinidinone (**1**).



Scheme 2. Reagents and conditions: (a) Li_2CuCl_4 (10 mol %), THF, −30 °C; butenylmagnesium bromide, 35 min, 88%; (b) TsCl (2 equiv), pyridine (1.9 equiv), CH_2Cl_2, 0 °C, 18 h, 90% (crude); (c) $BnNH_2$ (3 equiv), THF, reflux, 36 h, 86%.

* Corresponding author. Tel.: +421 2 5932 5162; fax: +421 2 5249 5381.
E-mail address: peter.szolcsanyi@stuba.sk (P. Szolcsányi).

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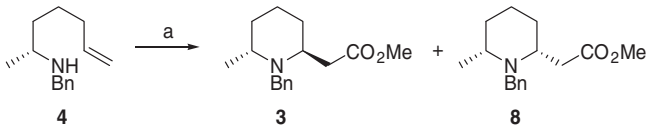


Scheme 3. Reagents and conditions: (a) CO (1 atm), $PdCl_2$ (10 mol %), $CuCl_2$ (3 equiv), AcONa (3 equiv), MeOH, 22 °C, 4 d, **3**/**8** (83/17), 58%.

With this promising initial result, we decided to perform extensive screening of the reaction conditions in order to find the optimal composition of catalytic mixture. Thus, we scrutinised the influence of the nature of the Pd(II)-salt, co-catalyst/re-oxidant, base and solvent on the yield of **3**/**8** as well as the diastereoselectivity of the methoxyaminocarbonylation. The results are summarised in Table 1.

In all successful cases (entries 1–21), the predominant formation of the 2,6-*trans*-configured piperidine **3** was observed.[7] The catalytic system based on 10 mol % $PdCl_2$ and excess $CuCl_2$ with either AcONa or Et_3N worked well (entries 1 and 2), while the employment of K_2CO_3 was less satisfactory (entry 3). The exclusion of base from the reaction mixture resulted in a dramatic drop in yield (entry 4). Similarly, a solvent change from MeOH to trimethyl orthoformate[4d] had a detrimental effect on the diastereoselectivity (entry 5). The use of $Pd(OAc)_2$, $Pd(OTFA)_2$ or Li_2PdCl_4 also gave reasonable levels of diastereoselectivity, however, the combined yields of the desired products were lower in these cases (entries 6–8). Moreover, the addition of two different chiral ligands under these conditions did not affect the diastereoselectivity at all (entries 10–12). Interestingly, a stoichiometric experiment employing 1 equiv of $PdCl_2$ without any re-oxidant required a higher temperature and longer reaction time to deliver the products, albeit in low yield (entry 9). This observation points to the dual role of $CuCl_2$ in the catalytic system being not only a re-oxidant but also an efficient co-catalyst. The use of aprotic co-solvents (THF, MeCN and/or 1,4-dioxane) along with MeOH (as the external nucleophile) maintained the good level of both yield and dr (entries 13–15). The best diastereoselectivity (80% dr.) was obtained with catalytic amounts of both $PdCl_2$ and $CuCl_2$ under 1 atm of CO/O_2 (ca. 1:1) using oxygen as the terminal oxidant in pure MeOH (entry 16), while the solvent mixtures performed less well (entries 17–21). Finally, changing $CuCl_2$ to either $Cu(OAc)_2$ or benzoquinone as re-oxidants furnished either a complex reaction mixture (entry 22) or undesired products (entries 23 and 24). Considering this along with the previous result (entry 9), the indispensable role of $CuCl_2$ as co-catalyst in this particular transformation is clear. However, the exact structure of the true catalytic species involved in our Pd(II)/$CuCl_2$-catalysed cyclisation-methoxyaminocarbonylation of **4** remains elusive. We assume that due to the metal composition under the optimal reaction conditions, it inevitably should be of a heterobimetallic nature. Such Pd/Cu-complexes in similar transformations involving both palladium and copper salts have been proposed and/or isolated and characterised.[8]

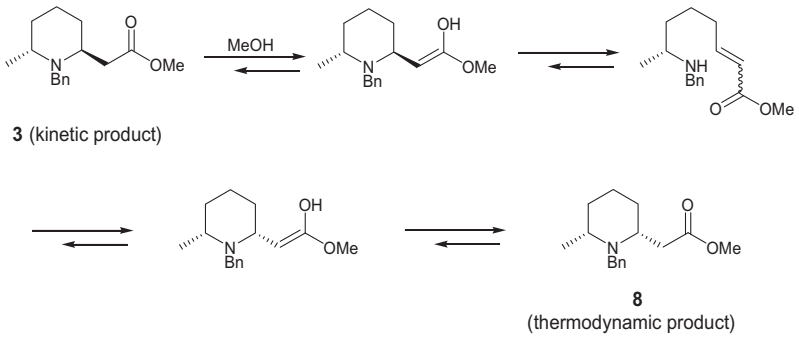
The preferential formation of the thermodynamically less stable product **3** in all cases is noteworthy, and as such, represents one of only a few examples where the 2,6-*trans*-configured piperidine having an ester group in the β-position is formed predominately.[9]

This is even more interesting considering the known fact that in protic media, including MeOH, similar compounds possessing a carbonyl-functionality may easily epimerise to their more stable *cis*-configured counterparts.[10] In order to assess the origin of the experimentally determined diastereoselectivities, we performed control experiments to test the possible epimerisation of **3** in methanol via a retro-*aza*-Michael addition type mechanism (Scheme 4).

Table 1
Pd(II)/$CuCl_2$-catalysed intramolecular methoxyaminocarbonylation of alkenyl amine **4**

Entry	Pd salt (0.1 equiv)	Re-oxidation system	Base (3 equiv)	Solvent	Temperature, time	Ratio[a] **3**/**8**, yield[b]
1	$PdCl_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	22 °C, 4 d	83/17, 58%
2	$PdCl_2$	$CuCl_2$ (3 equiv)	Et_3N	MeOH	21 °C, 2 d	78/22, 58%
3	$PdCl_2$	$CuCl_2$ (3 equiv)	K_2CO_3	MeOH	22 °C, 4 d	70/30, 40%
4	$PdCl_2$	$CuCl_2$ (3 equiv)	None	MeOH	30 °C, 2 d	61/39, 27%
5	$PdCl_2$	$CuCl_2$ (3 equiv)	None	$(MeO)_3CH$	40 °C, 2 d	59/41, 41%
6	$Pd(OAc)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	21 °C, 2 d	76/24, 47%
7	$Pd(OTFA)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	21 °C, 2 d	79/21, 42%
8	Li_2PdCl_4	$CuCl_2$ (3 equiv)	AcONa	MeOH	35 °C, 3 d	85/15, 40%
9[c]	$PdCl_2$	None	AcONa	MeOH	60 °C, 6 d	80/20, 36%
10[d]	$Pd(OTFA)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	30 °C, 2 d	80/20, 54%
11[d]	$Pd(OAc)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	30 °C, 2 d	80/20, 52%
12[e]	$Pd(OTFA)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH	30 °C, 2 d	83/17, 53%
13	$PdCl_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH/THF (1:1)	30 °C, 5 d	79/21, 53%
14	$PdCl_2(MeCN)_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH/MeCN (1:1)	25 °C, 3 d	84/16, 54%
15	$PdCl_2$	$CuCl_2$ (3 equiv)	AcONa	MeOH/1,4-dioxane (1:1)	23 °C, 3 d	75/25, 58%
16[f]	$PdCl_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH	22 °C, 24 h	90/10, 51%
17[f]	$PdCl_2(MeCN)_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH/MeCN (1:1)	30 °C, 3 d	72/28, 41%
18[f]	$PdCl_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH/1,4-dioxane (1:1)	21 °C, 2 d	69/31, 49%
19[f]	$PdCl_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH/DMF (1:1)	21 °C, 5 d	70/30, 52%
20[e,f]	$PdCl_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH/1,4-dioxane (1:1)	30 °C, 4 d	63/37, 58%
21[f]	$PdCl_2(PhCN)_2$	$CuCl_2$ (0.2 equiv)/O_2 (1 atm)	None	MeOH/1,4-dioxane (1:1)	40 °C, 4 d	69/31, 46%
22[g]	$Pd(OAc)_2$	$Cu(OAc)_2$ (3 equiv)	None	MeOH	50 °C, 2 d	—
23[h]	$Pd(OAc)_2$	Benzoquinone (1 equiv)	None	MeOH	36 °C, 3 d	—
24[h]	$PdCl_2$	Benzoquinone (1 equiv)	AcONa	MeOH	60 °C, 17 d	—

[a] Diastereomeric ratios were determined by GC analysis of the crude reaction mixture using an Agilent 5890 gas chromatograph equipped with an FID detector and split/splitless injector on a HP-5 column (50 m × 0.32 mm × 0.52 μm). The analyses were run in isothermic mode at 180 °C. (For **3**: t_R = 30.1 min, for **8**: t_R = 29.7 min.)
[b] Combined isolated yield of **3**+**8** after flash liquid chromatography (silica gel, toluene/EtOAc, 8:1 with 1% w/w NH_4OH).
[c] Stoichiometric amount of $PdCl_2$ was used.
[d] 3a*R*-[2(3′a*R**,8′a*S**),3′aβ,8′aβ]-(+)-2,2′-methylene-bis[3a,8a-dihydro-8*H*-indeno-[1,2-d]oxazole] (0.12 equiv) was used as a chiral ligand.
[e] (−)-Sparteine (0.12 equiv) was used as a chiral ligand.
[f] 3 Å molecular sieves were added.
[g] Full conversion of **4** with concomitant formation of a complex mixture of unidentified products.
[h] Full conversion of **4** without formation of piperidines **3** and/or **8**.

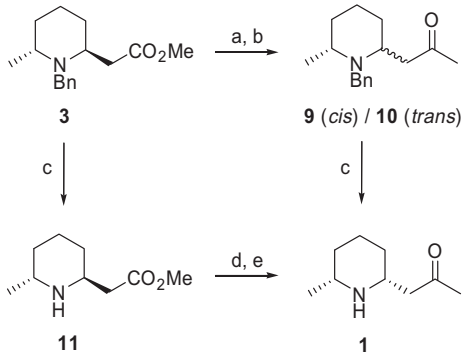


Scheme 4. The possible epimerisation of **3** into **8** in MeOH via a retro-*aza*-Michael type addition at elevated temperature.

We found that neither standing pure **3** in neat MeOH nor stirring its methanolic solution containing the Pd/Cu-catalytic system led to any observable epimerisation by TLC. However, raising the temperature above 60 °C resulted in slow but steady formation of **8** from **3**. As all our successful methoxyaminocarbonylations of **3** took place well below the critical temperature, we are confident that the observed diastereoselectivity is a result of the Pd/Cu-catalysed cyclisation only, and without any contribution from background epimerisation.

Having established reaction conditions[11] for the preparation of the desired piperidines **3**/**8**, we next focused on completion of the synthesis of **1**. The initially attempted direct conversion[12] of major ester **3** into ketone **9** using MeMgBr in the presence of Et_3N led only to complex mixtures. Therefore, we turned to the established methodology.[13a] Thus, treatment of **3** with Weinreb's reagent gave the crude *N*-methoxyamide, which was immediately treated[13b] with excess methylmagnesium bromide to yield a mixture of inseparable ketones **9** and **10** in a 1:2 ratio after flash liquid chromatography (FLC) using silica gel.[14] To check whether the epimerisation at C-2 during the Weinreb protocol/Grignard addition of **3** could be suppressed, we changed the order of the transformations. Thus, we first deprotected ester **3** using Pearlman's catalyst to obtain the piperidine **11** in 62% yield.[15] However, the subsequent transformation of 2,6-*trans*-disubstituted ester **11** into the corresponding ketone proceeded with complete epimerisation at C-2 after FLC using silica gel and furnished the 2,6-*cis*-configured naturally occurring alkaloid (−)-pinidinone **1**[1a,2] (Scheme 5).

Starting from commercially available (*S*)-propylene oxide (**6**), we have prepared (*R*)-benzyl-(1-methyl-hex-5-enyl)-amine (**4**) as a key substrate in three steps in 68% overall yield. Subsequently,



Scheme 5. Reagents and conditions: (a) 3 equiv MeNHOMe·HCl, 1.6 equiv Me_3Al, THF, 0 °C to rt, 18 h; (b) 2.3 equiv MeMgBr, THF, −78 °C to rt, 1 h, FLC (SiO_2), 30%, **9**/**10** (1:2); (c) H_2 (1 atm), $Pd(OH)_2$ (14 mol %), MeOH, rt, 18 h, FLC (SiO_2), **11** (62%), **1** (71%); (d) 3 equiv MeNHOMe·HCl, 3 equiv Me_3Al, THF, 0 °C to rt, 2.5 h, 74% crude; (e) 2.2 equiv MeMgBr, THF, −78 °C to rt, 1 h, FLC (SiO_2), 58%.

the alkenyl amine **4** was subjected to the broad reaction screening of the Pd(II)/$CuCl_2$-catalysed methoxyaminocarbonylation to furnish the desired cyclic esters **3**/**8**. The influence of the nature of the palladium and copper salts, the re-oxidant, the base and solvent on the yield of **3**/**8** as well as the diastereoselectivity was explored. We found that $CuCl_2$ was the optimum reagent for this transformation and acts not only as the re-oxidant, but also as an efficient co-catalyst in the presence of molecular oxygen as the terminal oxidant. The methyl ester **3** was subsequently used as a key intermediate in the total synthesis of the naturally occurring piperidine alkaloid (−)-pinidinone (**1**).

Acknowledgements

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10. It is reported that (+)-2-epipinidinone slowly epimerises to 2,6-*cis*-configured (−)- pinidinone (**1**) even on standing in MeOH at room temperature for a few days (see Ref. 1a). Such solution epimerisation was also reported for other piperidine alkaloids of similar structures, see, for example Fodor, G. B.; Colasanti, B. In *Alkaloids Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1985; Vol. 3, pp 49–73.
11. Typical procedure for the Pd(II)-catalysed aminocarbonylation: a suspension of aminoalkene **4** (200 mg, 0.984 mmol), $PdCl_2$ (17 mg, 0.0984 mmol, 0.1 equiv), $CuCl_2$ (397 mg, 2.95 mmol, 3 equiv) and AcONa (242 mg, 2.95 mmol, 3 equiv) in anhydrous MeOH (9.8 mL) was stirred under a CO atmosphere (balloon) at 22 °C over 4 d, while the colour of reaction mixture changed from turquoise to green. After evaporation, the residue was partitioned between AcOEt (20 mL) and 2% NH_4OH (20 mL). The aqueous layer was extracted with AcOEt (3×20 mL). The combined organic extracts were washed with brine (2×30 mL), dried over $MgSO_4$ and concentrated in vacuo. The brown oily residue was purified by careful flash liquid chromatography (SiO_2, toluene–AcOEt, 40:1 with 1% w/w NH_4OH) to furnish [(2*S*,6*R*)-1-benzyl-6-methyl-piperidin-2-yl]-acetic acid methyl ester (**3**) (109 mg, 42%) as a pale yellow oil and [(2*R*,6*R*)-1-benzyl-6-methyl-piperidin-2-yl]-acetic acid methyl ester **8** (40 mg, 16%) as a pale yellow oil.
Data for **3**: R_f = 0.73 (toluene–AcOEt, 8:1 with 1% w/w NH_4OH); $[\alpha]_D^{24}$ −3.9 (*c* 0.62, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): = 1.03 (d, $J_{Me,6}$ = 6.5 Hz, 3H, CH_3), 1.25–1.35 (m, 1H, H-5A), 1.38–1.44 (m, 1H, H-3A), 1.56–1.63 (m, 3H, H-4, H-5B), 1.66–1.70 (m, 1H, H-3B), 2.43 (dd, $J_{A,X}$ = 8.6, $J_{A,B}$ = 14.2 Hz, 1H, A of ABX, CH_2CO), 2.63 (dd, $J_{B,X}$ = 5.5, $J_{A,B}$ = 14.2 Hz, 1H, B of ABX, CH_2CO), 2.81–2.87 (m, 1H, H-6), 3.25–3.30 (m, 1H, H-2), 3.55 (d, *J* = 14.4 Hz, 1H, CH_2Ph), 3.60 (s, 3H, OCH_3), 3.81 (d, *J* = 14.4 Hz, 1H, CH_2Ph), 7.18–7.35 (m, 5H, Ph); ^{13}C NMR (150 MHz, $CDCl_3$): = 18.9 (q, CH_3), 19.6 (t, C-4), 28.0 (t, C-3), 31.6 (t, C-5), 34.2 (t, *C*H_2CO), 50.2 (d, C-6), 51.4 (q, OCH_3), 52.7 (t, *C*H_2Ph), 53.1 (d, C-2), 126.5 (d, C_p-Ph), 128.1 (d, $C_{o,m}$-Ph), 141.2 (s, C_q-Ph), 173.4 (s, C=O).
Data for **8**: R_f = 0.63 (toluene–AcOEt, 8:1 with 1% w/w NH_4OH); $[\alpha]_D^{25}$ −1.54 (*c* 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, $J_{Me,6}$ = 6.4 Hz, 3H, CH_3), 1.23–1.52 (m, 4H, H-3, H-5), 1.54–1.62 (m, 2H, H-4), 2.17 (dd, $J_{A,X}$ = 9.5, $J_{A,B}$ = 15.1 Hz, 1H, A of ABX, CH_2CO), 2.59 (dd, $J_{B,X}$ = 3.9, $J_{A,B}$ = 15.1 Hz, 1 H, B of ABX, CH_2CO), 2.68–2.72 (m, 1H, H-6), 2.95–3.09 (m, 1H, H-2), 3.58 (s, 3H, OCH_3), 3.71 (d, *J* = 17.0 Hz, 1H, CH_2Ph), 3.78 (d, *J* = 17.0 Hz, 1H, CH_2Ph), 7.12–7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): = 21.4 (q, CH_3), 22.9 (t, C-4), 30.4 (t, C-3), 32.6 (t, C-5), 40.3 (t, *C*H_2CO), 51.4 (d, C-6), 53.7 (q, OCH_3), 57.5 (t, *C*H_2Ph), 59.6 (d, C-2), 126.2 (d, C_p-Ph), 127.9 (d, $C_{o,m}$-Ph), 142.3 (s, C_q-Ph), 172.9 (s, C=O).
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14. The ^{1}H NMR spectra of the crude reaction mixture showed the formation of 2,6-*trans*-configured ketone **10** only. However, after purification of this material by flash liquid chromatography (SiO_2, toluene–AcOEt, 8:1 with 1% w/w NH_4OH) partial epimerisation of **10** into thermodynamically more stable **9** was observed.
15. Data for **11**: $[\alpha]_D^{25}$ +12.9 (*c* 0.29, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): = 1.08 (d, $J_{Me,6}$ = 6.4 Hz, 3H, CH_3), 1.18–1.23 (m, 1H, H-5A), 1.26–1.35 (m, 1H, H-3A), 1.49–1.56 (m, 1H, H-4A), 1.59–1.65 (m, 2H, H-4B, H-5B), 1.66–1.73 (m, 1H, H-3B), 1.85 (br s, 1H, exchange with D_2O, NH), 2.39 (dd, $J_{A,X}$ = 5.1, $J_{A,B}$ = 15.5 Hz, 1H, A of ABX, CH_2CO), 2.64 (dd, $J_{B,X}$ = 8.8, $J_{A,B}$ = 15.5 Hz, 1H, B of ABX, CH_2CO), 3.02–3.07 (m, 1 H, H-6), 3.44 (dt, J_{2,CH_2CO} = 5.1, $J_{2,3A}$ = $J_{2,3B}$ = 9.5 Hz, 1H, H-2), 3.69 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): = 19.5 (t, C-4), 21.3 (q, CH_3), 30.5 (t, C-3), 32.8 (t, C-5), 38.2 (t, *C*H_2CO), 45.6 (d, C-6), 48.1 (d, C-2), 51.5 (q, OCH_3), 173.1 (s, C=O). The relative 2,6-*trans*-configuration of **11** was confirmed on the basis of 1D NOESY experiments.