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Novel rearrangement of *N*-enoyl oxazolidinethiones to *N*-substituted 1,3-thiazine-2,4-diones promoted by $NbCl_5$

Hector Hernández,[a] Sylvain Bernès,[b] Leticia Quintero,[a] Estibaliz Sansinenea[b] and Aurelio Ortiz[a,*]

[a]*Centro de investigación, de la Facultad de Ciencias Químicas, de la Benemérita Universidad Autónoma de Puebla, Puebla Pue. 72570, Mexico*

[b]*Instituto de Ciencias, de la Benemérita Universidad Autónoma de Puebla, Puebla Pue. 72570, Mexico*

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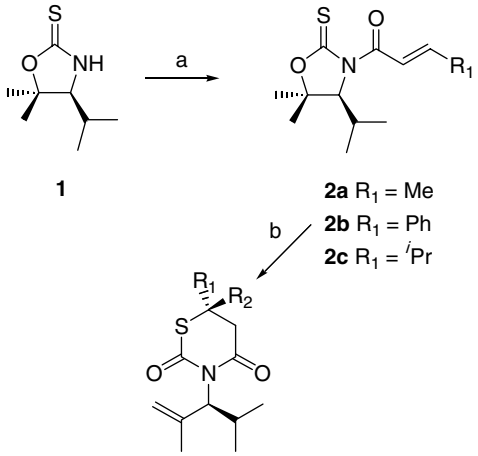
Abstract—$NbCl_5$ has been employed as promoter of a novel rearrangement to afford chiral *N*-substituted 1,3-thiazine-2,4-diones with one or two new stereogenic centers from di- and trisubstituted *N*-enoyl oxazolidinethiones. The trisubstituted *E*-isomers provide the *anti*-diastereomers mainly.

The six membered heterocyclic 1,3-thiazine-2,4-dione type has been the subject of great interest because of its different biological activities; for example, 5-ethyl-6-phenyl-1,3-thiazine-2,4-dione has been demonstrated to be an anesthetic agent, however also has exhibited undesirable side effects, as thrombophlebitis.[1] 3-(β-aminoethyl)-1,3-thiazine-2,4-dione hydrochloride has been reported to have antiradiation activity.[2] Substituted 1,3-thiazine-2,4-diones and 1,3-thiazine-4-ones were patented as useful sedatives, hypnotics, intravenous anesthetics, or anticonvulsants.[2]

Much of the research in heterocyclic chemistry is concerned with the development of new methods for ring syntheses. The synthesis of the 1,3-thiazine-2,4-dione ring has been performed by different methods, for example, condensation of thiourea with α,β-unsaturated carboxylic acids in phosphoric acid[3a] or sulfuric acid,[3b] addition reaction of ethylenethiourea,[4a] thiourea,[4b] ethyl thioglycolate,[4b] or *O*-ethyl allylthiocarbamate[4c] to β-haloacids. The first chiral 1,3-thiazinedione has been obtained by addition reaction of an oxazolidinethione to *N*-enoyl oxazolidinethione.[4d] In this letter we describe a novel rearrangement carried out with *N*-enoyl oxazolidinethiones using $NbCl_5$ as a promoter to provide chiral *N*-substituted 1,3-thiazine-2,4-diones.

Compounds (**2a**–**f**) were prepared from **1** as previously described.[5] Each of the compounds were added to a solution of (3.0 equiv) $NbCl_5$ in 100 mL of CH_2Cl_2 at −78 °C, followed by stirring at room temperature to provide the compounds (**3a**–**f**) as shown in Schemes 1 and 2.



3a R_1= Me R_2 = H **4a** R_1 = H R_2 = Me
3b R_1= Ph R_2 = H **4b** R_1= H R_2 = Ph
3c R_1 = ^{i}Pr R_2 = H **4c** R_1 = H R_2 = ^{i}Pr

Scheme 1. Reagents and conditions: (a) NaH, $R_1CHCHCOCl$, 0 °C CH_2Cl_2; (b) $NbCl_5$ (3.0 equiv), CH_2Cl_2, rt.

* Corresponding author. Tel.: +52 222 2295500x7518; fax: +52 222 2295584; e-mail: jaortizm@siu.buap.mx

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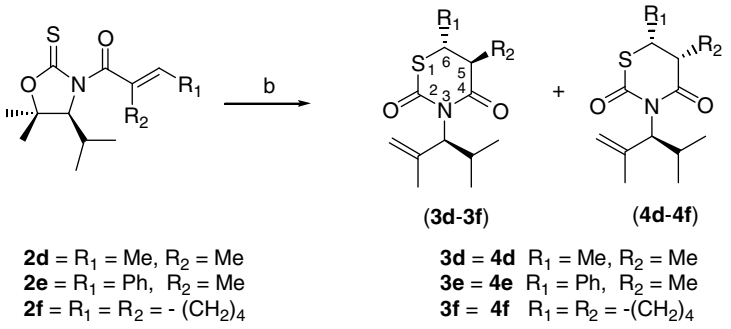


Scheme 2. Reagents: (b) $NbCl_5$ 3.0 equiv, CH_2Cl_2, H_2O.

This rearrangement was carried out with di-(**2a**–**c**) and trisubstituted *N*-enoyl oxazolidinethiones (**2d**–**f**) to provide heterocyclic compounds with one (**3a**–**c**) or two (**3d**–**f**) new chiral centers (Scheme 2), in a range of 16–87% yield, all of them as colorless liquids, except for **3f** and **4e** as white solid compounds. The results of these reactions are shown in Table 1.

Table 1. Rearrangement of *N*-enoyl oxazolidinethiones

Products	*t* (h)[a]	Yield (%)[b]	dr (**3**:**4**)[c]
3a/**4a**	48	60.0	98/2
3b/**4b**	12	87.0	98/2
3c/**4c**	48	18.0	98/2
3d/**4d**	14	16.0	83/17
3e/**4e**	16	55.0	60/40
3f/**4f**	12	82.0	96/4

[a] *t* = time.
[b] Purified yield.
[c] Diastereomeric isomer ratios were determined by ^1H and ^{13}C NMR on the crude products.

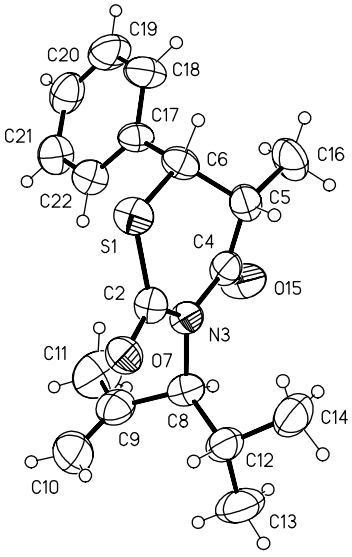


Figure 1. Molecular structure of adduct **4e**.

From the data in Table 1, it was observed that the formation of new chiral centers in compounds **3a**–**c** and **3f** is highly diastereoselective, however in the case of compounds **3d** and **3e** there is a notable difference in the diastereomeric isomer ratios maybe because the formation of the second new chiral center is through a diastereoselective protonation reaction, giving at room temperature modest diastereoselectivity. The stereochemical outcome of the major diastereomers can be rationalized by comparison of the $^3J_{HH}$ values for thiazines (**3d**–**f** and **4e**) and the use of a generalized Karplus type relationship[6] that allowed to establish the relative configuration of the two newly created stereogenic centers as *anti* for **3d**–**f** and *syn* for **4e** (as shown in Table 2). The absolute configuration at the newly formed stereogenic centers (C-5, C-6) are *R* and *S*, respectively, as established by X-ray analysis of the minority compound **4e** (Fig. 1),[7]

Table 2. Comparison of the vicinal coupling constants

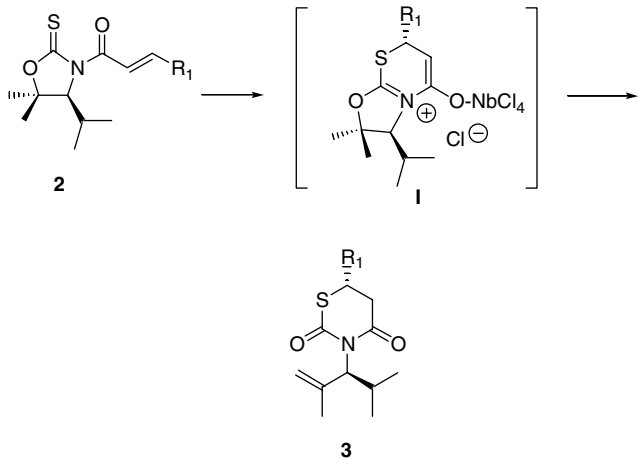
Products	$^3J_{H\text{-}5\text{-}H\text{-}6}$ (Hz)	Dihedral angle (°)
3d-(5*S*,6*R*)	7.2	139
3e-(5*S*,6*S*)	10.2	155
3f-(5*S*,6*R*)	12.0	170
4e-(5*R*,6*S*)	4.2	51

which is homologous to β-mercapto, the compound previously described.[5]

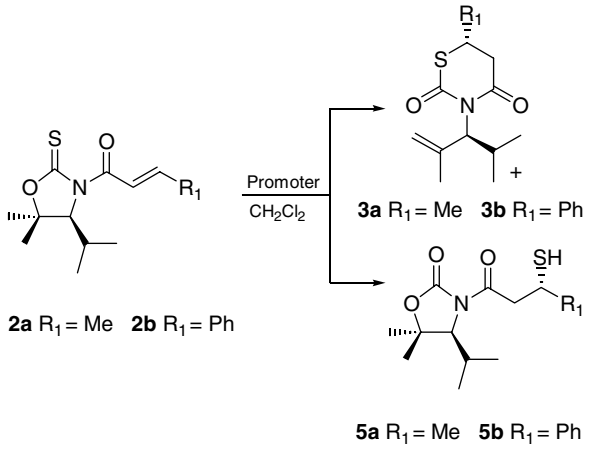
Absolute configuration for majority compounds (**3a**–**f**) was assigned on the basis of the comparison between the 1,3-thiazines and the β-mercapto compounds previously described.[5] The formation of **3** can be explained by the previous formation of the immonium ion **I**,[5c] which is obtained by an intramolecular sulfur transfer to C(β) in the *N*-enoyl oxazolidinethione **2** as a plausible conjecture. The unexpected elimination reaction led to the formation of the double bond in **3** as shown in Scheme 3.

The rearrangement was explored using the compounds **2a** and **2b** employing different amounts of promoter to provide the thiazines (**3a**,**b**) or β-mercapto carbonyl adducts[5a] (**5a**,**b**) as shown in Scheme 4. The results of these reactions are shown in Table 3.

From the data in Table 3, it was observed that the formation of the thiazines **3a** and **3b** was carried out through a competitive reaction to the formation of the β-mercapto carbonyl adducts (**5a** and **5b**). When 3 equiv of $NbCl_5$ was used, the thiazine ring was favored while the use of 1.2 equiv lead to well known β-mercapto com-



Scheme 3. Possible course of the transformation of **2** to **3**.



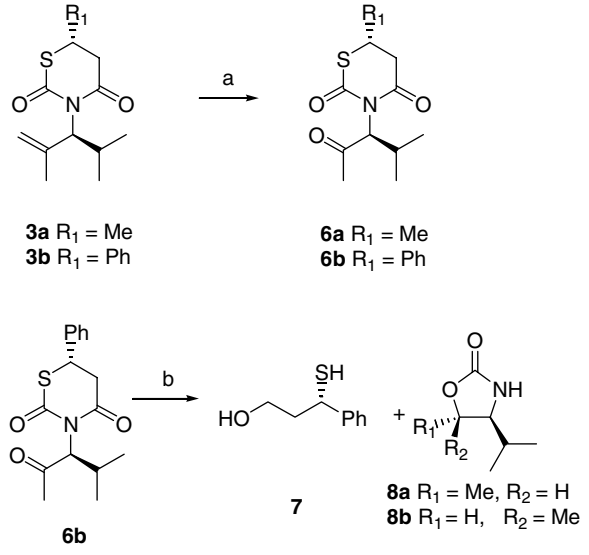
Scheme 4.

Table 3. Optimization of the reaction of **2a** and **2b**

Compound	Promoter (equiv)	*T* (°C)/*t* (h)	Yield[a] **3/5**	dr[b]
2a	$SnCl_4$ (1.2)	25/12	0/40	70/30
2a	$SnCl_4$ (3.0)	25/18	0/43	69/31
2a	$NbCl_5$ (1.2)	25/12	0/45	68/32
2a	$NbCl_5$ (2.0)	25/12	15/24	90/10
2a	$NbCl_5$ (3.0)	25/48	60/0	98/2
2b	$NbCl_5$ (1.2)	25/14	60/0	76/24
2b	$NbCl_5$ (1.2)	40/2	40/0	57/43
2b	$NbCl_5$ (2.0)	25/14	40/50	80/20
2b	$NbCl_5$ (3.0)	40/4	82/15	98/2
2b	$NbCl_5$ (3.0)	25/12	87/0	98/2

[a] Purified yield.
[b] Diastereomeric isomer ratios were determined by ^1H and ^{13}C NMR on the crude products of the major diastereoisomer.

pound.[5] We also studied the effect of the temperature: at 40 °C in **2b** with 1.2 and 3.0 equiv of $NbCl_5$, it was observed that the reaction was oriented preferably to product **3b** in a shorter reaction time than at room temperature. Compound **2a** was treated with 1.2 and 3.0 equiv of $SnCl_4$ at rt, and in both cases provided a diastereomeric mixture of β-mercapto adducts **5a**. For the formation of the double bond in the thiazines we currently do not have a rational explanation, since the rearrangement was further investigated using **2b** with 3 equiv of $NbCl_5$ and 1.5 equiv of NEt_3 to provide the thiazine **3b** in 60% yield in a reaction time of 6 h. Thiazines **3a** and **3b** were treated with 3 equiv of $NaIO_4$ and a catalytic amount of OsO_4 in THF/H_2O, to provide ketones **6a** and **6b** in 46% and 50% yield, respectively. To ketone **6b** was added $NaBH_4$ in MeOH at 0 °C to provide a diastereomeric mixture of (4*S*,5*S*)-**8a** and (4*S*,5*R*)-4-isopropyl-5-methyl oxazolidinone[10] **8b** in a ratio 60:40, and the respective mercapto alcohol **7** in 44% yield, $[\alpha]_D^{25}$ −45 (*c* 0.5, $CHCl_3$) as shown in Scheme 5.



Scheme 5. Reagents: (a) $NaIO_4$, OsO_4, THF/H_2O; (b) $NaBH_4$, MeOH.

Complete assignment[11] of the ^1H and ^{13}C NMR spectra of **3a–f** and **4e** was achieved by 2D proton–proton and 2D carbon–proton correlated experiments.

In conclusion we have found that $NbCl_5$ is an excellent promoter of a new rearrangement that was carried out in *N*-enoyl oxazolidinethiones to give chiral *N*-substituted 1,3-thiazine-2,4-diones with one or two new chiral centers. The *E*-isomers **2d–f** provide the *anti*-diastereoisomers, **3d–f** as main products.

Acknowledgments

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7. *Crystal data for* **4e**: $C_{18}H_{23}NO_2S$, $M = 317.43$, colorless plate, $0.60 \times 0.20 \times 0.08$ mm^3, space group $C2$, cell parameters $a = 22.097$ (4), $b = 8.6353$ (15), $c = 20.372$ (3) Å, $\beta = 109.32$ (2)°, $Z = 8$, $Z' = 2$, $D_c = 1.150$ g cm^{-3}, 9384 reflections collected on a Bruker P4 diffractometer at room temp., with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 3.78$–50.00°, of which 4786 are unique ($R_{int} = 0.039$), 407 variables refined: $R_1 = 0.0424$ [2723 data with $I > 2\sigma(I)$] and $wR_2 = 0.1235$ [all data].[8] Absolute configuration was determined starting from the known configuration at C8 and confirmed by the refinement of a Flack parameter based on 1354 measured Friedel pairs, $\chi = 0.02(15)$.[9] Complete data have been deposited with the CCDC, reference 289253. Structure factors and raw files are available on request to authors.
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11. Compound **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.02 (1H, s, H-1′), 5.00 (1H, s, H-1′), 4.77 (1H, d, $J = 11.6$ Hz, H-3′), 3.40 (1H, m, H-6), 2.97 (1H, dd, $J = 4.4$, 16.4 Hz, H-5), 2.72 (1H, dd, $J = 8.8$, 14.8 Hz, H-5), 2.70 (1H, m, H-4′), 1.65 (3H, s, CH_3-2′), 1.33 (3H, d, $J = 6.0$ Hz, CH_3-6), 0.90 (3H, d, $J = 7.2$ Hz, CH_3-5′), 0.75 (3H, d, $J = 7.2$ Hz, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2 (CO), 168.3 (CO), 140.6 (C-2′), 116.1 (C-1′), 65.0 (C-3′), 43.0 (C-5), 31.8 (C-6), 26.6 (C-4′), 21.7 (CH_3-2′), 21.2 (CH_3-5′), 20.6 (CH_3-4′), 19.4 (CH_3-5′). $[\alpha]_D^{25}$ −39.5 (*c* 2.1, $CHCl_3$).
Compound **3b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (5H, m, Ph), 5.12 (1H, s, H-1′), 5.07 (1H, s, H-1′), 4.86 (1H, d, $J = 10.8$ Hz, H-3′), 4.60 (1H, dd, $J = 5.1$, 9.6 Hz, H-6), 3.28 (2H, m, H-5), 2.77 (1H, m, H-4′), 1.71 (3H, s, CH_3-2′), 0.98 (3H, d, $J = 6.6$ Hz, CH_3-5′), 0.84 (3H, d, $J = 6.6$ Hz, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1 (CO), 168.5 (CO), 141.0 (C-2′), 136.4 (*Ci*), 129.2 (C*m*), 128.8 (C*p*), 127.2 (C*o*), 116.4 (C-1′), 65.4 (C-3′), 42.7 (C-5), 40.7 (C-6), 26.5 (C-4′), 21.7 (CH_3-2′), 21.2 (CH_3-5′), 19.6 (CH_3-5′). $[\alpha]_D^{25}$ −21.7 (*c* 1.2, $CHCl_3$).
Compound **3c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 (1H, s, H-1′), 5.05 (1H, s, H-1′), 4.83 (1H, d, $J = 11.2$ Hz, H-3′), 3.17 (1H, ddd, $J = 3.3$, 7.2, 10.0 Hz, H-6), 3.04 (1H, dd, $J = 3.6$, 15.2 Hz, H-5), 2.75 (1H, m, H-4′), 1.86 (1H, m, CH-6), 1.73 (3H, s, CH_3-2′), 1.05 (3H, d, $J = 6.0$ Hz, CH_3), 1.04 (3H, d, $J = 6.4$ Hz, CH_3), 0.97 (3H, d, $J = 6.4$ Hz, CH_3-4′), 0.82 (3H, d, $J = 6.4$ Hz, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2 (CO), 169.1 (CO), 141.3 (C-2′), 116.4 (C-1′), 65.2 (C-3′), 44.0 (C-6), 39.4 (C-5), 26.6 (C-4′), 32.2 (CH-6), 22.0 (CH_3-2′), 21.3(CH_3-5′), 19.7 (CH_3), 19.6 (CH_3-4′), 19.5 (CH_3), $[\alpha]_D^{25}$ −15.1 (*c* 0.9, $CHCl_3$).
Compound **3d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 (1H, s, H-1′), 5.06 (1H, s, H-1′), 4.85 (1H, d, $J = 10.8$ Hz, H-3′), 3.10 (1H, dq, $J = 6.8$, 7.2 Hz, H-6), 2.85 (1H, dq, $J = 6.8$, 7.2 Hz, H-5), 2.76 (1H, m, H-4′), 1.71 (3H, s, CH_3-2′), 1.45 (3H, d, $J = 6.8$ Hz, CH_3-6), 1.40 (3H, d, $J = 6.8$ Hz, CH_3-5), 0.97 (3H, d, $J = 6.4$ Hz, CH_3-5′), 0.84 (3H, d, $J = 6.8$ Hz, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7 (2CO), 140.5 (C-2′), 116.0 (C-1′), 65.0 (C-3′), 45.6 (C-6), 38.1 (C-5), 27.1 (C-4′), 21.8 (C-2′), 21.4 (C-8), 21.4 (C-5′), 19.4 (C-4′), 15.4 (C-7). $[\alpha]_D^{25}$ −49.9 (*c* 1.3, $CHCl_3$).
Compound **3e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (5H, m, Ph), 5.11 (1H, s, H-1′), 5.06 (1H, s, H-1′), 4.86 (1H, d, $J = 10.8$ Hz, H-3′), 4.23 (1H, d, $J = 10.2$ Hz, H-6), 3.24 (1H, dq, $J = 10.2$, 6.9 Hz, H-5), 2.75 (1H, m, H-4′), 1.73 (3H, s, CH_3-2′), 1.18 (3H, d, $J = 6.9$ Hz, CH_3-5), 0.98 (3H, d, $J = 6.6$ Hz, CH_3-4′), 0.84 (3H, d, $J = 6.6$ Hz, CH_3-5′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.0 (CO), 169.0 (CO), 141.1 (C-2′), 136.3 (C*i*), 129.0 (C*m*), 128.7 (C*p*), 128.5 (C*o*), 116.2 (C-1′), 66.0 (C-3′), 47.1 (C-6), 45.4 (C-5), 26.3 (C-4′), 21.6 (CH_3-2′), 21.1 (CH_3-4′), 19.4 (CH_3-5′), 14.7 (CH_3-5). $[\alpha]_D^{25}$ +7.77 (*c* 1.6, $CHCl_3$).
Compound **4e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (3H, m, Ph),7.23 (2H, m, Ph), 5.14 (1H, s, H-1′), 5.11 (1H, s , H-1′), 4.92 (1H, d, $J = 11.1$ Hz, H-3′), 4.60 (1H, d, $J = 4.2$ Hz, H-6), 3.30 (1H, qd, $J = 6.9$, 4.2 Hz, H-5), 2.82 (1H, m, H-4′), 1.76 (3H, s, CH_3-2′), 1.22 (3H, d, $J = 6.9$ Hz, CH_3-5), 0.98 (3H, d, $J = 6.6$ Hz,CH_3-5′), 0.86 (3H, d, $J = 6.6$ Hz,CH_3-5′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3 (CO), 168.5 (CO), 140.7 (C-2′), 135.5 (C*i*), 129.0 (C*m*), 128.6 (C*p*), 127.8 (C*o*), 116.6 (C-1′), 65.7 (C-3′), 45.7 (C-6), 44.3 (C-5), 26.8 (C-4′), 21.6 (CH_3-2′), 21.2 (CH_3-5′), 19.6 (CH_3-5′), 12.7 (CH_3-5). $[\alpha]_D^{25}$ −89.6 (*c* 1.9, $CHCl_3$). Mp 52 °C.
Compound **3f**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.06 (1H, s, H-1′), 5.00 (1H, s, H-1′), 4.80 (1H, d, $J = 10.0$ Hz, H-3′), 3.20 (1H, ddd, $J = 4.0$, 11.6, 12.0 Hz, H-6), 2.70 (1H, m, H-4′), 2.50 (1H, ddd, $J = 4.0$, 11.6, 12.0, H-5), 2.30 (1H, m, H-7e), 1.97, 1H, m, H-10e), 1.91 (1H, m, H-8e), 1.84 (1H, m, H-9e), 1.71 (3H, s, CH_3-2′), 1.45–1.28 (4H, br, H-7_{ax}–H-10_{ax}) 0.96 (3H, d, $J = 6.4$ Hz, CH_3-5′), 0.80 (3H, d, $J = 6.4$ Hz, CH_3-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5 (CO), 168.1 (CO), 141.4 (C-2′), 116.0 (C-1′), 65.8 (C-3′), 47.7 (C-5), 39.6 (C-6), 31.5 (C-10), 27.1 (C-7), 26.0 (C-4′), 25.0 (C-8), 25.0 (C-9), 21.6 (CH_3-2′), 21.3 (CH_3-5′), 19.6 (CH_3-5′). $[\alpha]_D^{25}$ −60.1 (*c* 2.8, $CHCl_3$). Mp 32 °C.