

INTRAMOLECULAR CYCLOADDITIONS WITH ISOBENZOFURANS - XII¹ - SYNTHESIS AND REACTIONS OF FURO[3,4-*d*]ISOXAZOLES

Stephan Reck^a, Karsten Bluhm^b, Tony Debaerdemaeker^c, Jean-Paul Declercq^d,
Burkhard Klenke^a, and Willy Friedrichsen^{*a}

^aInstitut für Organische Chemie der Universität, Otto-Hahn-Platz 4, D-24098 Kiel,
Germany

^bInstitut für Anorganische Chemie der Universität, Otto-Hahn-Platz 6/7, D-24098
Kiel, Germany

^cSektion für Röntgen- und Elektronenbeugung der Universität, Oberer Eselsberg 3,
D-89081 Ulm, Germany

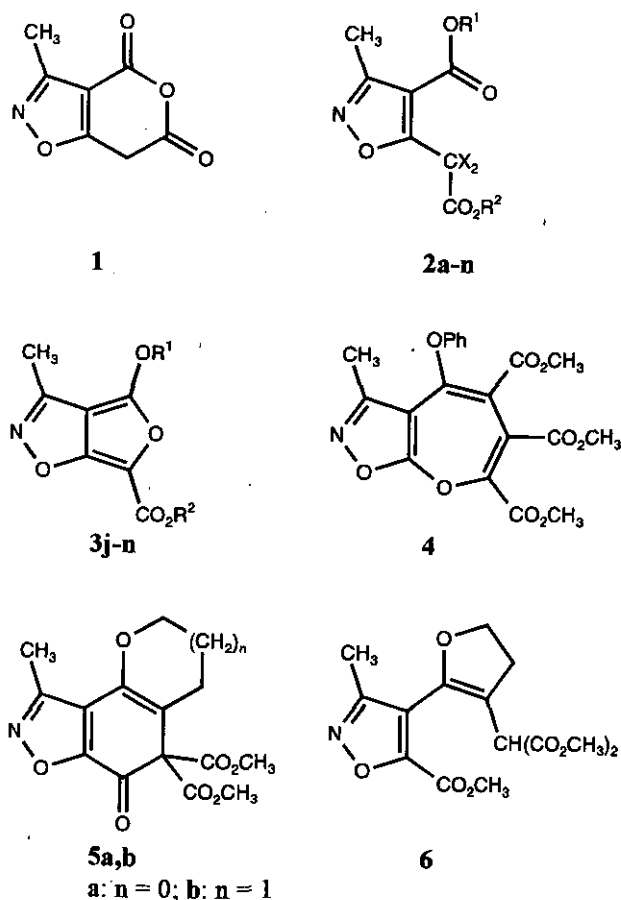
^dUniversité Catholique de Louvain, Laboratoire de Chimie et de Cristallographie 1,
Place Louis Pasteur, B-1348 Louvain-la-Neuve, Belgium

Abstract - The synthesis of furo[3,4-*d*]isoxazoles (**3**) and inter- and intramolecular cycloaddition reactions (to **4**, **5a,b**) are reported. The structures of **3k**, **5b** and **6** have been clarified by X-ray crystallography. Quantum chemical calculations (AM1, PM3, *ab initio*, density functional methods) concerning the geometry and the different reactivity of benzo[*c*]furans and furo[3,4-*d*]isoxazoles were performed.

Furo[3,4-*d*]isoxazoles (e.g., **3**) are virtually unknown,² although without any doubt these species are involved as intermediates in the synthesis of annulated isoxazoles.^{3,4} In this paper we report the generation and reaction of compounds of this type. Regioselective solvolytic ring opening of anhydride (**1**) with methanol yields **2b**;³ this compound can also be obtained from acid (**2a**) by selective esterification (MeOH/H₂SO₄; 89%). Subsequent treatment with phenol/DMAP/DCC⁵ yields **2e**⁶ (50%, colorless oil; ir (film): 1743 cm⁻¹; ¹H nmr (CDCl₃): δ = 2.55 ppm (s, 3H, CH₃), 3.74 (s, 3H, CO₂CH₃), 4.21 (s, 2H, CH₂), 7.13-7.17 (m, 2H, *o*-arCH), 7.25-7.31 (m, 1H, *p*-arCH), 7.39-7.46 (m, 2H, *m*-arCH)), which was reacted with tosyl azide/triethylamine(MeCN, room temperature)⁷ to give **2j** (86%; yellow crystals, mp 70°C; ir (KBr): 2136 cm⁻¹, 1727, 1715; ¹H nmr (CDCl₃): δ = 2.56 ppm (s, 3H, CH₃), 3.88 (s, 3H, CO₂CH₃), 7.14-7.19 (m, 2H, *o*-arCH), 7.26-7.33 (m, 1H, *p*-arCH), 7.40-7.47 (m, 2H, *m*-arCH)). It is well known that nitrogen extrusion from compounds of this type yields *c*-annulated furans (*Hamaguchi-Ibata* reaction).⁸ Treatment of **2j** with Rh₂(OAc)₄ (0.9 mol%, 1,2-dichloroethane, reflux, 75 min) yields **3j** (72%, colorless crystals, mp 119°C; ir (KBr): 1715 cm⁻¹, 1648; uv (MeCN) λ (log ε): 212 nm (4.261), 258 (sh, 4.099), 266 (4.139), 295 (4.319); ¹H nmr (CDCl₃): δ = 1.55 ppm (s, 3H, CH₃),⁹ 3.91 (s, 3H, CO₂CH₃), 7.26-7.31 (m, 2H, *o*-arCH),

7.36-7.42 (m, 1H, *p*-arCH), 7.48-7.55 (m, 2H, *m*-arCH); ^{13}C nmr (CDCl_3): δ = 10.07 ppm (q, CH_3), 51.57 (q, CO_2CH_3), 102.64 (s, C-3a), 111.84 (s, C-6), 120.16 (d, *o*-arC), 127.39 (d, *p*-arC), 130.76 (d, *m*-arC), 147.85 (s, C-6a), 151.25 (s, C-3), 153.83 (s, *O*-arC), 157.33 (s, CO_2CH_3), 161.59 (s, C-4)), which on reaction with DMAD (CHCl_3 , reflux, 3 h) gives an oxepino[3,2-*d*]isoxazole (**4**) (38%, slightly yellow crystals, mp 147°C; ir (KBr): 1739 cm^{-1} , 1617; uv (MeCN) λ (log ϵ): 215 nm (4.495), 325 (3.789); ^1H nmr (CDCl_3): δ = 2.05 ppm (s, 3H, CH_3), 3.55 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 6.96-7.01 (m, 2H, *o*-arCH), 7.07-7.13 (m, 1H, *p*-arCH), 7.26-7.36 (m, 2H, *m*-arCH)).

Scheme 1.

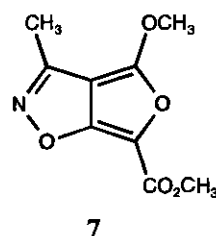
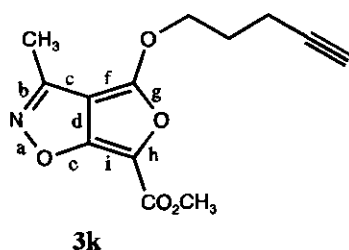


2, 3	X	R ¹	R ²
a	H	H	H
b	H	H	CH ₃
c	H	CH ₃	CH ₃
d	H	CH ₃	H
e	H	Ph	CH ₃
f	H	-(CH ₂) ₃ -C≡CH	CH ₃
g	H	-(CH ₂) ₃ -C≡C-CO ₂ CH ₃	CH ₃
h	H	-(CH ₂) ₂ -C≡C-CO ₂ CH ₃	CH ₃
i	H	CH ₃	-CH ₂ -C≡CH
j	N	Ph	CH ₃
k	N	-(CH ₂) ₃ -C≡CH	CH ₃
l	N	-(CH ₂) ₃ -C≡C-CO ₂ CH ₃	CH ₃
m	N	-(CH ₂) ₂ -C≡C-CO ₂ CH ₃	CH ₃
n	N	CH ₃	-CH ₂ -C≡CH

Furoisoxazole (**3k**) was prepared quite similarly by reaction of **2b** with 4-pentyn-1-ol using again the *Neises-Steglich* conditions⁵ and treatment of **2k**¹² with $\text{Rh}_2(\text{OAc})_4$ (0.8 mol%, 1,2-dichloroethane, reflux, 3 h). The compound was obtained as fine colorless needles with mp 75°C.¹³ An X-ray investigation of **3k**¹⁴ reveals that the heterocyclic ring system is essentially planar. Quantum chemical calculations on the semiempirical (AM1, PM3)^{10a} as well as the *ab initio*^{10b} and the density functional¹⁹⁻²¹ level show (Table 1) that the latter methods - especially, when Becke's three parameter²² DFT exchange functional in combination with the Lee, Yang,

and Parr correlation functional (BECKE3LYP)²³ together with a 6-31 G* basis^{10b} is used - lead to a very good agreement between experimental and calculated values.

Table 1: Bond distances (in Å) of **3k** and **7** (obs. vs. calc.).^{a,b}



bond	AM1 ^c	PM3 ^c	RHF/6-31G* ^d	RHF/6-311G** ^d	BLYP/6-31G* ^d	BECKE3LYP/6-31G* ^d	obs. ^{c,e}
a	1.347	1.517	1.407	1.401	1.485	1.445	1.474
b	1.341	1.319	1.275	1.272	1.323	1.307	1.300
c	1.456	1.446	1.449	1.443	1.442	1.437	1.432
d	1.479	1.457	1.402	1.402	1.424	1.413	1.395
e	1.389	1.355	1.318	1.315	1.357	1.342	1.348
f	1.378	1.379	1.361	1.360	1.391	1.380	1.372
g	1.387	1.375	1.307	1.304	1.362	1.342	1.345
h	1.432	1.416	1.403	1.402	1.434	1.414	1.412
i	1.371	1.376	1.354	1.353	1.388	1.376	1.361

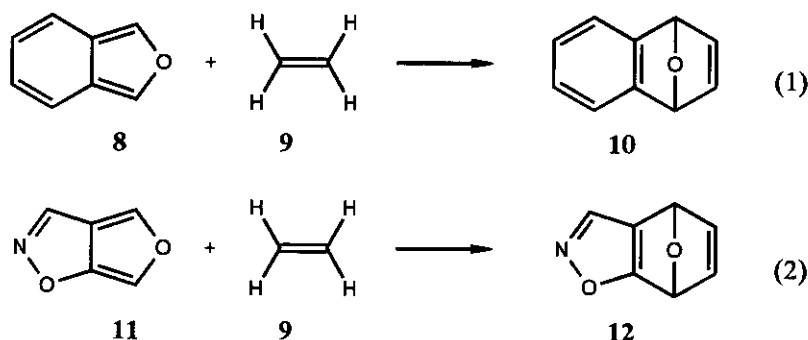
^a Semiempirical calculations (AM1, PM3) were performed with the program system MOPAC.¹⁶ ^b *Ab initio* calculations were performed with the program systems GAUSSIAN92¹⁷ and GAUSSIAN92/DFT.¹⁸ ^c For **3k**. ^d For **7**. ^e X-ray.

Interestingly enough **3k** did not undergo an intramolecular cycloaddition as did **3l** (*vide infra*). If (as in **3l**, **m**) the furoisoxazole carries an electron deficient triple bond spontaneous intramolecular cycloaddition reactions are observed. The preparation of **2l** was accomplished by reaction of **2b** with methyl 6-hydroxyhex-2-yn-1-carboxylate²⁴/DMAP/DCC⁵ (to get **2g**²⁵) and subsequent diazgroup transfer.^{7,26} Nitrogen extrusion ($\text{Rh}_2(\text{OAc})_4$, toluene, reflux, 5 h) resulted in the formation of **5b**.²⁷ Quite obviously a furoisoxazol (**3l**) is generated in the first step. Intramolecular cycloaddition with subsequent ring opening yields **5b**.²⁸ The structure of **5b** has been clarified definitely by X-ray crystallography.²⁹ Compound (**5a**) was prepared quite similarly by reaction of **1b** with methyl 5-hydroxypentyn-1-carboxylate²⁴/DMAP/DCC⁵ (to **2h**³⁰), subsequent diazgroup transfer⁷ (to **2m**),³¹ and decomposition (0.5 mol% $\text{Rh}_2(\text{OAc})_4$, 1,2-dichloroethane, reflux, 2 h). If during workup (chromatography) methanol is used as eluent compound (**6**)³² is obtained. The formation

of **6** can be rationalized by solvolytic ring opening reaction of **5a**. It is also possible to prepare furoisoxazoles with an unsaturated moiety at C-6 (e. g., **3n**). Selective saponification of **2c**, which is in turn available from **2a** ($\text{SOCl}_2/\text{MeOH}/40^\circ\text{C}$; colorless oil, 75%) with potassium hydroxide/MeOH (reflux, 4 h),³³ esterification with 2-propyn-1-ol/DMAP/DCC⁵ (to **2i**),³⁴ diazogroup transfer⁷ (to **2n**)³⁵ and subsequent treatment with $\text{Rh}_2(\text{OAc})_4$ (0.49 mol%, 1,2-dichloroethane, reflux, 2 h) yields **3n**.³⁶

Generally speaking in $[\pi 4 + \pi 2]$ cycloadditions furo[3,4-*d*]isoxazoles are less reactive than the corresponding benzo[*c*]furans (isobenzofurans).³⁷ These findings are in line with expectations. Following a similar reasoning as Rickborn and coworkers³⁸ on various levels of theory (semiempirical, *ab initio*, density functional theory) the calculated exothermicity of reaction (2) ($\Delta\Delta H_f^\circ(1) = \Delta H_f^\circ(10) - (\Delta H_f^\circ(8) + \Delta H_f^\circ(9))$ or $\Delta E(1) = \Delta E(10) - (E(8) + E(9))$, resp.) is less than the corresponding value of reaction (1) (Table 2).

Table 2: Calculated reaction enthalpies ($\Delta\Delta H_f^\circ$) and reaction energies (ΔE) for reactions (1) and (2).



method	$\Delta\Delta H(1) (\Delta E(1))^a$	$\Delta\Delta H(2) (\Delta E(2))^a$	$\Delta\Delta\Delta H (\Delta\Delta E)^{a,c}$
AM1	34.8	22.9	11.9
PM3	32.5	21.1	11.4
6-31G*	36.9	28.0	8.9
MP2/6-31G**/6-31G*	44.3	37.4	6.9
DFT ^b	21.5	12.2	9.3

^a In kcal/mol. ^b Density functional method (BLYP/6-31G*); ^c $\Delta\Delta\Delta H(\Delta\Delta E) = \Delta\Delta H(1) (\Delta E(1)) - \Delta\Delta H(2) (\Delta E(2))$.

ACKNOWLEDGEMENT

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11. According to these calculations there are at least two different conformers of **3j** ($\text{C}(6)\text{CH}_3\text{-Ph}$: syn (AM1: -22.9 kcal/mol; PM3: -54.7 kcal/mol); $\text{C}(6)\text{CH}_3\text{-Ph}$: anti (AM1: -23.4 kcal/mol; PM3: -52.8 kcal/mol)) (ΔH_f° values).
12. **2f**: 56%, colorless oil; ir (film): 1748 cm^{-1} , 1722; ^1H nmr (CDCl_3): δ =1.95 ppm (tt, 2H, $^3J_1=6.4$ Hz, $^3J_2=7.0$ Hz, $\text{CH}_2\text{-CH}_2\text{-CH}_2$) 2.00 (t, 1H, $^4J=2.7$ Hz, $\text{C}=\text{CH}$), 2.34 (td, 2H, $^3J_1=7.0$ Hz, $^4J_2=2.7$ Hz, $\text{CH}_2\text{-C}=\text{CH}$), 2.49 (s, 3H, CH_3), 3.75 (s, 3H, CO_2CH_3), 4.15 (s, 2H, $\text{CH}_2\text{CO}_2\text{CH}_3$), 4.39 (t, 2H, $^3J=6.3$ Hz, OCH_2). - **2k**: 83%, yellow oil; ir (film): 2130 cm^{-1} , 1725, 1714.
13. **3k**: ir (KBr): 3267 cm^{-1} , 1702, 1654, 1595; uv (MeCN) λ (log ϵ): 214 nm (4.311), 267 (4.199), 295 (4.289); ^1H nmr (CDCl_3): δ =2.02 ppm (t, 1H, $J=2.7$ Hz, $\text{-C}=\text{CH}$), 2.01-2.15 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-C}=\text{CH}$), 2.38-2.47 (m, 2H, $\text{-CH}_2\text{-C}=\text{CH}$), 2.43 (s, 3H, CH_3), 4.63 (t, 2H, $J=6.1$ Hz, OCH_2); ^{13}C nmr (CDCl_3): δ = 11.18 ppm (q, CH_3), 14.86 (t, $\text{CH}_2\text{-C}=\text{CH}$), 27.76 (t, $\text{CH}_2\text{-CH}_2\text{-C}=\text{CH}$), 51.37 (q, CO_2CH_3), 69.86 (d, $\text{C}=\text{CH}$), 70.97 (t, OCH_2), 82.01 (s, $\text{C}=\text{CH}$), 101.17 (s, C-3a), 111.59 (s, C-6), 148.81 (s, C-4), 151.18 (s, C-3), 157.40 (s, CO_2CH_3), 162.38 (s, C-6a); ms (70 eV): calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: 263.0793, found 263.0792.
14. Space group $\text{P}\bar{1}$. Cell dimensions: $a = 10.1710$ (13) Å, $b = 10.729$ (3) Å, $c = 13.429$ (2) Å, $\alpha = 69.070^\circ$ (14), $\beta = 86.220^\circ$ (11), $\gamma = 66.270^\circ$ (13). CSD number¹⁵: 404654.
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25. **2g**: Colorless oil, 62%; ir (film): 2238 cm^{-1} , 1744; ^1H nmr (CDCl_3): δ = 2.02 ppm (tt, 2H, $J_1=7.2$ Hz, $J_2=6.2$ Hz, $\text{CH}_2\text{-CH}_2$).

- CH₂), 2.48 (s, 3H, CH₃), 2.50 (t, 2H, J=7.2 Hz, CH₂-C=C), 3.75 (s, 6H, CO₂CH₃), 4.13 (s, 2H, CH₂-CO₂CH₃), 4.37 (t, 2H, J=6.2 Hz, OCH₂).
26. **2l**: Yellow oil, 83%; ir (film): 2238 cm⁻¹, 2131, 1735, 1714; ¹H nmr (CDCl₃): δ = 2.03 ppm (tt, 2H, J₁=6.3 Hz, J₂=7.1 Hz, CH₂-CH₂-CH₂), 2.46 (s, 3H, CH₃), 2.50 (t, 2H, J=7.1 Hz, CH₂-C=C), 3.75 (s, 3H, CO₂CH₃), 3.90 (s, 3H, CO₂CH₃), 4.40 (t, 2H, J=6.3 Hz, OCH₂).
27. **5b**: Yellow crystals, mp 161°C, 17%; ir (KBr): 1751 cm⁻¹, 1737; ¹H nmr (CDCl₃): δ = 1.96-2.05 ppm (m, 2H, CH₂-CH₂-CH₂), 2.24-2.30 (m, 2H, OCH₂-CH₂-CH₂), 2.50 (s, 3H, CH₃), 3.80 (s, 6H, CO₂CH₃), 4.19-4.25 (m, 2H, OCH₂); ¹³C nmr (CDCl₃): δ = 11.25 ppm (q, CH₃), 21.60 (t, C-7), 22.02 (t, C-6), 53.66 (q, CO₂CH₃), 66.43 (t, C-5), 74.24 (s, C-8), 109.26 (s, C-7a), 124.95 (s, C-3a), 142.27 (s, C-3b), 156.69 (s, C-3), 156.98 (s, C-9a), 164.98 (s, CO₂CH₃), 177.87 (s, C-9).
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29. Space group: P2₁/a. Cell dimensions: a = 8.458 (2) Å, b = 17.842 (6) Å, c = 10.518 (2) Å, α = 90°, β = 110.11° (2), γ = 90°. CSD number¹⁵: 404649.
30. **2h**: Colorless oil, 69%; ir (film): 2242 cm⁻¹, 1747, 1719; ¹H nmr (CDCl₃): δ = 2.50 ppm (s, 3H, CH₃), 2.78 (t, 2H, J=6.3 Hz, CH₂-C=C), 3.74 (s, 3H, CO₂CH₃), 3.76 (s, 3H, CO₂CH₃), 4.15 (s, 2H, CH₂-CO₂CH₃), 4.41 (t, 2H, J=6.3 Hz, OCH₂).
31. **2m**: Fine yellow needles, mp 84°C, 80%; ir (KBr): 2242 cm⁻¹, 2137, 1725, 1707; ¹H nmr (CDCl₃): δ = 2.48 ppm (s, 3H, CH₃), 2.80 (t, 2H, J=6.3 Hz, CH₂-C=C), 3.77 (s, 3H, CO₂CH₃), 3.88 (s, 3H, CO₂CH₃), 4.42 (t, 2H, J=6.3 Hz, OCH₂).
32. **6**: Colorless needles, mp 102°C; ir (KBr): 1750 cm⁻¹, 1726, 1613; ¹H nmr (CDCl₃): δ = 2.31 (s, 3H, CH₃), 3.06 (t, 2H, J=9.6 Hz, CH₂-C=C), 3.75 (s, 6H, CO₂CH₃), 3.91 (s, 3H, CO₂CH₃), 4.04 (s, 1H, CH), 4.53 (t, 2H, J=9.6 Hz, OCH₂); ¹³C nmr (CDCl₃): δ = 10.34 (q, CH₃), 31.59 (t, CH₂-CH₂-C=C), 50.09 (d, CH), 52.71 (q, CO₂CH₃), 52.93 (q, CO₂CH₃), 70.17 (t, CH₂-CH₂-C=C), 109.34 (s, CH₂-CH₂-C=C), 114.36 (s, C-4), 143.30 (s, CH₂-CH₂-C=C), 156.60 (s, C-5), 156.81 (s, C-3), 161.10 (s, CO₂CH₃), 167.85 (s, CO₂CH₃). - X-ray data: Space group P1. Cell dimensions: a = 7.873 (2) Å, b = 13.382 (4) Å, c = 16.028 (2) Å, α = 108.34° (2), β = 90.42° (2), γ = 97.92° (2). CSD number¹⁵: 404749.
33. **2d**: ir (KBr): 3600-2800 cm⁻¹, 1718, 1618; ¹H nmr (CDCl₃): δ = 2.45 ppm (s, 3H, CH₃), 3.85 (s, 3H, CO₂CH₃), 4.10 (s, 2H, CH₂), 9.56 (s, 1H, CO₂H); ¹³C nmr (DMSO-d₆): δ = 11.09 ppm (q, CH₃), 33.09 (t, CH₂-CO₂CH₃), 52.66 (q, OCH₃), 109.46 (s, C-4), 159.29 (s, C-3), 161.68 (s, CO₂CH₃), 168.22 (s, C-5), 171.56 (s, CO₂H).
34. **2i**: Colorless oil, 62%; ir (film): 2128 cm⁻¹, 1753, 1729; ¹H nmr (CDCl₃): δ = 2.47 (s, 3H, CH₃), 2.50 (t, 1H, ⁴J=2.5 Hz, C=CH), 3.86 (s, 3H, CO₂CH₃), 4.16 (s, 2H, CH₂-CO), 4.75 (d, 2H, ⁴J=2.5 Hz, OCH₂).
35. **2n**: Yellow oil, 96%; ir (film): 2135 cm⁻¹, 1726, 1714; ¹H nmr (CDCl₃): δ = 2.46 (s, 3H, CH₃), 2.53 (t, 1H, ⁴J=2.5 Hz, C=CH), 3.88 (s, 3H, CO₂CH₃), 4.89 (d, 2H, ⁴J=2.5 Hz, OCH₂).
36. **3n**: Colorless needles, mp 139°C, 68%; ir (KBr): 3252 cm⁻¹, 2126, 1710, 1648; uv (MeCN) λ (log ε): 213 nm (4.321), 268 (4.172), 294 (4.295); ¹H nmr (CDCl₃): δ = 2.42 ppm (s, 3H, CH₃), 2.51 (t, 1H, ⁴J=2.5 Hz, C=CH), 4.23 (s, 3H, OCH₃), 4.88 (d, 2H, ⁴J=2.5 Hz, OCH₂); ¹³C nmr (CDCl₃): δ = 11.06 (q, CH₃), 51.64 (q, OCH₃), 58.74 (t, OCH₂), 74.91 (d, C=CH), 77.91 (s, C=CH), 110.11 (s, C-3a), 111.28 (s, C-6), 149.74 (s, C-4), 151.28 (s, C-3), 155.97 (s, CO₂CH₂), 163.27 (s, C-6a).
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