Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 191–194

Synthesis and cardiovascular activity of metoprolol analogues

Roberto Melgar-Fernández,[a,d] Patricia Demare,[a] Enrique Hong,[b] Miguel Angel Rosas,[b] Jaime Escalante,[c] Omar Muñoz-Muñiz,[d] Eusebio Juaristi[d] and Ignacio Regla[a,*]

[a]*Facultad de Estudios Superiores-Zaragoza, Universidad Nacional Autónoma de México, 09230 México, D.F., Mexico*
[b]*Departamento de Farmacobiología, Centro de Investigación y de Estudios Avanzados del IPN, Apartado Postal 22-026, 14000 México, D.F., Mexico*
[c]*Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, 62210 Cuernavaca, Mor., Mexico*
[d]*Departamento de Química, Centro de Investigación y de Estudios Avanzados del IPN, Apartado Postal 14-740, 07000 México, D.F., Mexico*

Received 25 March 2003; revised 5 September 2003; accepted 27 September 2003

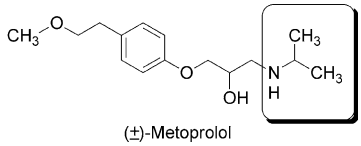
Abstract—The synthesis of four novel analogues of metoprolol, a well-known β_1-blocker used to reduce arterial blood pressure, is described. The preparation of (2*S*,2′*S*)-**7**, (2*R*,2′*S*)-**7**, (2*R*,2′*R*)-**8**, and (2*S*,2′*R*)-**8** was based on the reaction of racemic 2-[4-(2′-methoxyethyl)-phenoxymethyl]-oxirane (**4**) with (*R*)- or (*S*)-2-amino-1-butanol. Salient characteristics of analogues **7** and **8** relative to metoprolol are the incorporation of an additional stereogenic center, as well as a methyl group and a hydroxyl function on the nitrogen-containing chain. These novel derivatives present significant hypotensive and bradycardiac activity, although no blocking action toward β_1 and β_2 adrenergic receptor.

1. Introduction

Hypertension results from an increase of both systolic and diastolic blood pressure, that causes damage in cardiac, renal, and brain blood vessels.[1] The consequences of this irregularity are rather serious; for example, cardiovascular illnesses presently affect over 10 million people in Mexico, being the number one cause of death in the country.[2] It has been demonstrated that proper control of arterial blood pressure by means of pharmaceutical agents decrease the harmful blood vessel damage mentioned above. Thus, various drugs are used to lower arterial blood pressure, and among these, adrenergic β-blockers are particularly effective.[3]

Metoprolol has been and still is one of the most frequently used β-blocker agents. This drug is lipophilic, cardioselective, and exhibits a marked selectivity toward β_1 adrenergic receptors —the type of receptors that predominate in cardiac muscles. The efficacy of metoprolol in the treatment of hypertension, angina pectoris and cardiac heart failure is ascribed to β_1 blockade of catecholamines, which are endogenous substances that provoke an increase in blood pressure and induce myocardial contraction.[4]

Several studies of the pharmacokinetics[5,6] as well as secondary affects[7] exhibited by both enantiomers of metoprolol have revealed eudismic ratios (ER) of the order of 270 in favor of the (*S*) enantiomer, while undesirable side effects such as dizziness and delution are associated to the (*R*) enantiomer. Nevertheless, metoprolol is commercialized as a racemate.



(±)-Metoprolol

In recent years, the search for new active derivatives of metoprolol led to the preparation of a number of fluorinated analogues, but unfortunately those derivatives present low activity.[8]

Here, we want to describe the synthesis of four new derivatives of metoprolol, containing two stereogenic centers. Figure 1 emphasizes the structural changes being introduced in derivatives **7** and **8**: one of the diastereotopic[9,10]

* Corresponding author. Tel.: +52-55-5623-0727; fax: +52-55-5642-8977; e-mail: regla@servidor.unam.mx

0960-894X/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2003.09.070

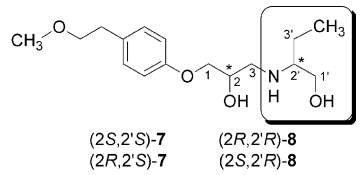


Figure 1. Stereoisomeric analogues of metoprolol prepared in this work.

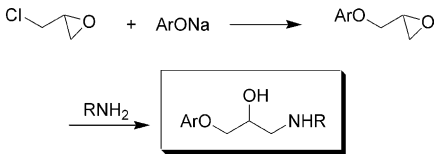
methyl groups in metoprolol becomes an ethyl group, whereas the other diastereotopic methyl group is now hydroxylated.

It is appreciated that derivatives **7** and **8** maintain the aryloxypropanolamino framework, that is essential for pharmacological activity in Propranolol and other drugs.[11]

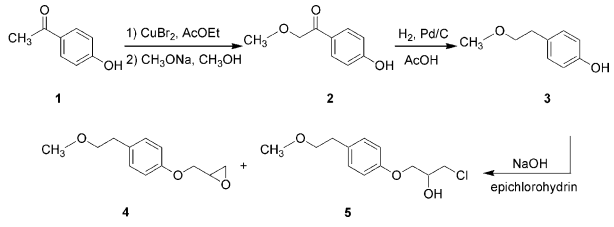
The traditional route[6,12] for the construction of the aryloxypropanolamino framework involves the addition of phenolic nucleophiles to epichlorohydrin in basic media to afford an aryloxyepoxipropane derivative that is subjected to aminolysis as shown in Scheme 1.

The first step in our synthetic route consisted in the preparation of 4-(2-methoxyethyl)phenol (**3**), according to the procedure of Smith and co-workers.[13] Treatment of phenol derivative **3** with racemic epichlorohydrin in aqueous sodium hydroxide solution afforded the desired 2-[4-(2′-methoxyethyl)-phenoxymethyl]-oxirane (**4**) in 90% yield (Scheme 2). This reaction produced chlorohydrin **5** as side product (10% yield), that was easily removed by silica gel column chromatography.

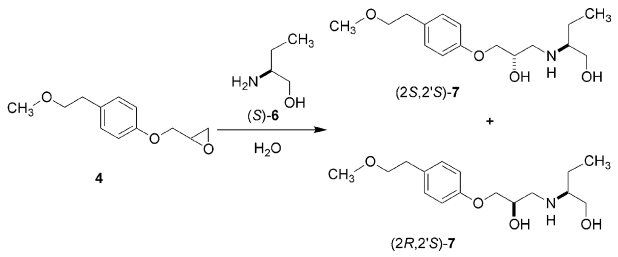
Treatment of racemic epoxide **4** with excess (*S*)-2-amino-1-butanol, (*S*)-**6**, in aqueous solution gave the desired diastereomeric derivatives (2*S*,2′*S*)-**7** and (2*R*,2′*S*)-**7** (Scheme 3). Gratifyingly, the *like*[9] diastereomer crystallized from the aqueous solution in essentially pure form. Diastereomeric product (2*R*,2′*S*)-**7** was isolated from the mother liquor following distillation of the remaining amine (*S*)-**6**. Furthermore, suitable crystals of (2*R*,2′*S*)-**7** were obtained in this fashion, that permitted X-ray diffraction determination of the *relative* configuration in this isomer (Fig. 2).



Scheme 1.



Scheme 2.



Scheme 3.

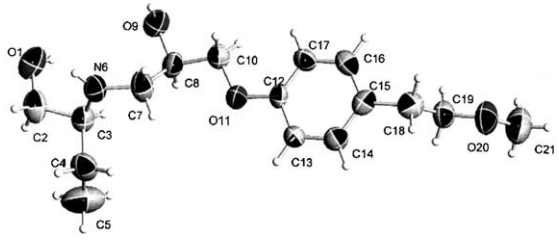


Figure 2. Structure and solid-state conformation of (2*R*,2′*S*)-**7**.[14]

Scheme 3 summarizes the synthetic protocol developed for the preparation of diastereomeric aminodiols **7**. The same procedure, but using (*R*)-**6** instead of (*S*)-**6**, was followed for the synthesis of (2*R*,2′*R*)-**8** and (2*S*,2′*R*)-**8**.

As expected, enantiomeric pairs (2*S*,2′*S*)-**7**/(2*R*,2′*R*)-**8** and (2*R*,2′*S*)-**7**/(2*S*,2′*R*)-**8** showed similar melting points and magnitude of the optical rotation (opposite sign).[15] Final characterization was completed by ^{1}H and ^{13}C NMR, infrared spectroscopy, and mass spectrometry.[16]

2. Cardiovascular activity

All four derivatives (2*S*,2′*S*)-**7**, (2*R*,2′*S*)-**7**, (2*R*,2′*R*)-**8**, and (2*S*,2′*R*)-**8** were initially evaluated in vivo, as potential blockers of β-adrenergic receptors in an 'invasive' type test, performed cannulating a carotid artery and a femoral vein. Isoproterenol was used as agonist for β_1- and β_2-adrenergic receptors, since this agent is known to lower medium arterial pressure (MAP) and to increase heart rate (HR). Tests were conducted in untreated male rats. The procedure was the following: (1) atropine (0.1 mg/kg) was administered via intraperitoneal route (ip), followed by sodium pentobarbital (ip) to sedate the animal. (2) A tracheotomy was performed to ventilate the incision and then both the carotid artery and femoral vein were cannulated. (3) The carotid artery was connected to a pressure transductor Mod. P23 coupled to a Grass Polygraph Mod. 7D. Heparin was administered at this moment to prevent coagulation. (4) Isoproterenol (0.31 μg/kg) was administered via femoral vein injection, before and after treatment with the test compounds (0.1, 0.31, 1.0, 3.1 mL/kg of 10^{-2} M solution). (5) MAP and HR readings were recorded after the administration of Isoproterenol and following treatment with the test compounds.

Exposure to metoprolol resulted in two types of effects: one of them consisted in decrease of arterial pressure, accompanied by short-term bradycardiac activity. The

other effect resulted in inhibition of the response produced by isoproterenol on MAP and HR. This second effect was more pronounced, which is typical of β_1 antagonists (Fig. 3). The lowering in arterial blood pressure induced by metoprolol was proportional to the dose being administered, and it is likely due to the negative chronotropic and inotropic effects produced by the adrenergic antagonist. Although this biological test is not specific to cardiac arrhythmia, a decrease in the frequency and strength of cardiac contraction is frequently associated to antiarrhythmic drugs. On the other hand, the lack of dose response in the negative chronotropic effect of metoprolol suggests that this is not an ideal antiarrhythmic agent.

All four derivatives (2*S*,2′*S*)-**7**, (2*R*,2′*S*)-**7**, (2*R*,2′*R*)-**8**, and (2*S*,2′*R*)-**8** presented hypotensive effects at high-level dose, that does not modify the isoproterenol-induced response, although it is accompanied by a decrease in MAP. Interestingly, the four compounds exhibited a better HR response. In this regard, (2*S*,2′*R*)-**8** and (2*S*,2′*S*)-**7**, showed a lineal dose-response behavior, whereas (2*R*,2′*R*)-**8**, and (2*R*,2′*S*)-**7** exhibited logarithmic-type behavior. Nevertheless, no compound exhibited affinity for the β_1- and β_2-adrenergic receptors, since they were not able to revert the effect induced by Isoproterenol (Figs. 4 and 5).

Thus, incorporation of a hydroxy group and extension of methyl to ethyl in the metoprolol structure modified its blocking effect, affording compounds with moderate

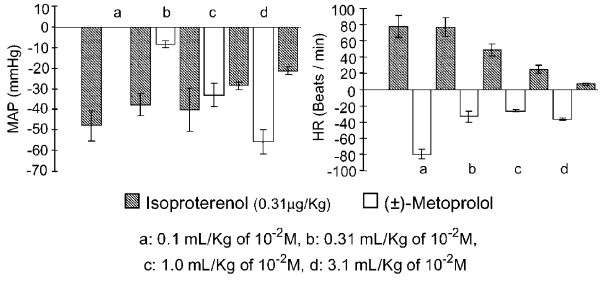


Figure 3. MAP and HR responses to (±)-metoprolol.

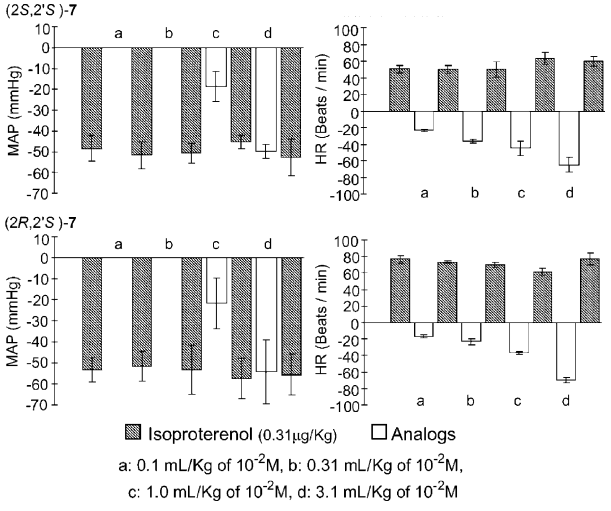


Figure 4. MAP and HR responses to isomeric **7**.

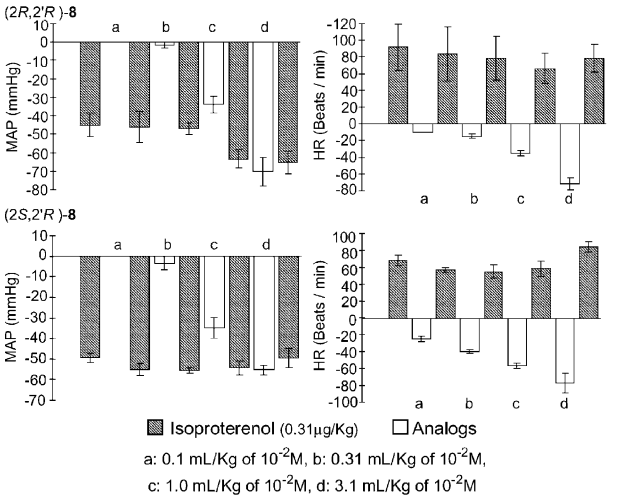


Figure 5. MAP and HR responses to isomeric **8**.

hypotensive activity and antiarrhythmic activity potential. This potential antiarrhythmic activity may be due to pharmacological mechanisms similar to those established for (+)-propranolol, which is interpreted in terms of membrane structure stabilization.[17]

In vitro tests were performed on isolated aorta rings, obtained from male rats, and placed in 2.0 mL assay chambers containing Krebs solution at 37 °C and continuously bubbled with a 95:5 oxygen–CO_2 gas mixture. Following a 2-h stabilizing period, the aorta rings were subjected to one of three protocols: (a) rings were incubated with 1.0×10^{-4} M *N*-nitro-L-arginine methyl ester (L-NAME, well-known inhibitor of nitric oxide synthase) and then put in contact with the test compounds ($c=1.0\times10^{-3}$ M). (b) Rings were incubated with 80 mM of potassium and then exposed to either metoprolol or the test compounds ($c=1.0\times10^{-3}$ M). (c) The rings were incubated with Krebs solution devoid of calcium but previously treated with 80 mM of potassium. At this point, tissue contractions were induced by addition of increasing amounts of calcium ions, in the presence or absence of the compounds being tested ($c=1.0\times10^{-3}$ M). Results from these experiments are presented in Figures 6 and 7.

The observations collected in Figures 6 and 7 indicate that the new compounds do not present β-blocker activity. Nevertheless, the results show short-lasting hypotensive and bradycardizant effects that can be explained in terms of nitric oxide release and inhibition

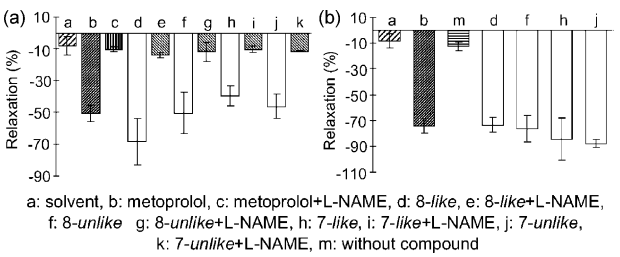


Figure 6. (a) Relaxation responses in the presence or absence of L-NAME. (b) Relaxation responses in the presence of potassium ions.

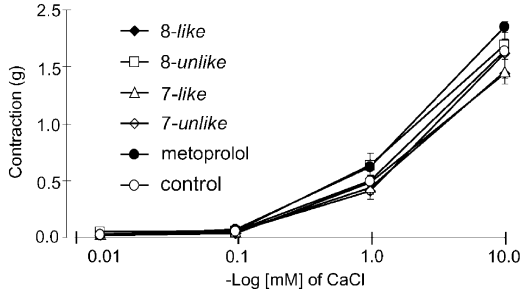


Figure 7. (c) Contraction responses induced by increasing concentrations of calcium ions.

of calcium access to cells. In particular, (2*S*,2′*S*)-**7** and (2*S*,2′*R*)-**8**, presenting the (*S*) configuration at C(2), seem to be most effective to mimic the desired biological effect of eutomeric (*S*)-metoprolol.

Acknowledgements

We are indebted to IXON, S. A., México, for financial support, and to Mr. Julio Sánchez Martínez for technical assistance.

References and notes

1. Brody, T.; Larner, J.; Minneman, K. *Human Pharmacology*, 3rd ed.; Mosby: St. Louis, 1998.
2. Mexican Ministry of Health. Principales Causas de Mortalidad General en los Estados Unidos Mexicanos; INEGI: 1999. http://www.ssa.gob.mx, July 26, 2001.
3. Teerlink, J.; Massie, B. *Am. J. Cardiol.* **1999**, *84*, 94.
4. Johnson, G.; Forssman, O. *Cardiovascular Information, β-Blocker and Cardiac Arrhythmias*; AB Hässle: Mölndal, Sweden, 1981.
5. Mostafavi, S.; Foster, R. T. *Int. J. Pharm.* **2000**, *202*, 97.
6. Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993.
7. Young, J. W. and Barberich, T. J. European Patent 0 677, 291, A2, 1995
8. Iseki, K.; Oishi, S.; Sasai, H.; Shibasaki, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1273.
9. Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; J. Wiley: New York, 1991.
10. Eliel, E.; Wilen, H. *Stereochemistry of Organic Compounds*; J. Wiley: New York, 1994.
11. Gurjar, M. K.; Shreerang, V. J.; Sastry, B. S.; Rama-Rao, A. V. *Synthetic Commun.* **1990**, *20*, 3489.
12. Luch, J. R. *Analytical Profiles of Drug Substances*; Florey: New York, 1983; Vol. 12, p 325.
13. Smith, B. L., Mueller, W. H. and Strutz, H. European Patent 0, 449, 602, A1, 1991
14. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk). Deposition number: CCDC 206055.
15. Physical properties: (2*S*,2′*S*)-**7**, mp 109–110 °C; $[\alpha]_D^{20} = +10.3$ (c1, CH_3OH). (2*R*,2′*S*)-**7**, mp 74–75 °C; $[\alpha]_D^{20} = +10.3$ (c1, CH_3OH). (2*R*,2′*R*)-**8**, mp 109–110 °C; $[\alpha]_D^{20} = -10.8$ (c1, CH_3OH). (2*S*,2′*R*)-**8**, mp 74–75 °C; $[\alpha]_D^{20} = -10.8$ (c1, CH_3OH).
16. **4-(2-methoxyethyl)phenol (3).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.85 (t, *J* = 7.1 Hz, 2H), 3.42 (s, 3H), 3.64 (t, *J* = 7.5 Hz, 2H), 6.75 (d, *J* = 11 Hz, 2H), 7.05 (d, *J* = 11 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ: 35.27, 58.65, 74.17, 115.53, 130.05, 130.45, 154.55. **2-[4-(2′-methoxyethyl)-phenoxymethyl]-oxirane (4).** η = 1.519 (25 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.82 (t, *J* = 7.1 Hz, 2H), 2.74, 2.89 (dd, *J* = 5.1, 2H), 3.32 (m, 1H), 3.34 (s, 3H), 3.56 (t, *J* = 6.9 Hz, 2H), 3.92, 4.18 (dd, *J* = 11.2 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 35.31, 40.74, 50.21, 58.66, 68.80, 73.82, 114.57, 129.83, 131.64, 156.99. **General experimental procedure for the preparation of (2*S*,2′*S*)-7, (2*R*,2′*S*)-7, (2*R*,2′*R*)-8, and (2*S*,2′*R*)-8.** In a 50-mL round-bottom flask was placed 8.9 g (0.1 mol) of (*S*)-**6** and 8.9 mL of water. The resulting solution was treated with 2.7 g (0.013 mol) of (±)-**4** and the reaction mixture was stirred at ambient temperature for 24 h. 5 mL of water was added and the resulting precipitate was filtered, washed with water, and air-dried to afford 1.9 g of crude product, which was recrystallized from 10 mL of ethyl acetate to give 1.65 g (43% yield) of (2*S*,2′*S*)-**7**. The mother liquor was heated at reduced pressure to recover excess (*S*)-**6** (bp 35–40 °C/4 mmHg) and the residue was dissolved in 10 mL of hot water. Upon cooling, a precipitate formed, that was rinsed with cold water and air-dried to furnish 1.3 g of crude product, which was recrystallized from 10 mL of ethyl acetate to give 0.95 g (25% yield) of (2*R*,2′*S*)-**7**. **(2*S*,2′*S*)-7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, *J* = 7.6 Hz, 3H), 1.41, 1.49 (ddq, *J* = 7.3, 13.9 Hz, 2H), 2.54 (m, *J* = 5.4, 12 Hz, 2H), 2.67, 2.93 (dd, *J* = 12 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 3.33 (s, 3H), 3.38, 3.64 (dd, *J* = 5, 11 Hz, 2H), 3.54 (t, *J* = 7.3 Hz, 2H), 3.92 (dd, 2H), 4.06 (m, *J* = 4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 10.44, 24.12, 35.27, 49.26, 58.63, 60.70, 63.02, 69.18, 70.55, 73.83, 114.53, 129.85, 131.45, 157.15. EM; *m*/*z* (%), 298 (M + 1, 12), 266 (100), 102 (65.7), 72 (23.7). IR ν_{max} (KBr), cm^{-1}: 3349, 2917, 1616, 1514, 1244, 1100, 1044, 822. **(2*R*,2′*S*)-7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (t, *J* = 7.3 Hz, 3H), 1.40, 1.48 (ddc, *J* = 6.9, 17.2 Hz, 2H), 2.54 (m, *J* = 6.9, 9.9 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 4H), 3.33 (s, 3H), 3.37, 3.64 (dd, *J* = 7.4, 11 Hz, 2H), 3.54 (t, *J* = 6.9 Hz, 2H), 3.92 (d, *J* = 5.1 Hz, 2H), 4.05 (m, *J* = 5.8, 11 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ: 10.44, 24.21, 35.27, 49.17, 58.65, 60.60, 63.06, 69.07, 70.58, 73.83, 114.49, 129.82, 131.48, 157.08. IR ν_{max} (KBr), cm^{-1}: 3355, 2917, 1611, 1516, 1244, 1100, 825.
17. Murray, K.; Reilly, C.; Koshakji, R.; Roden, D.; Lineberry, M.; Word, A.; Siddoway, I.; Barbey, J.; Woosley, R. *J. Clin. Invest.* **1990**, *85*, 836.