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Oxidation of α-Oxo-Oximes to Nitrile Oxides with Hypervalent Iodine Reagents

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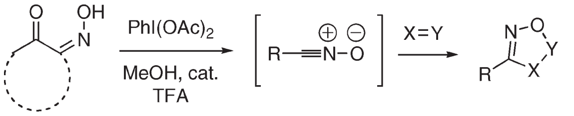
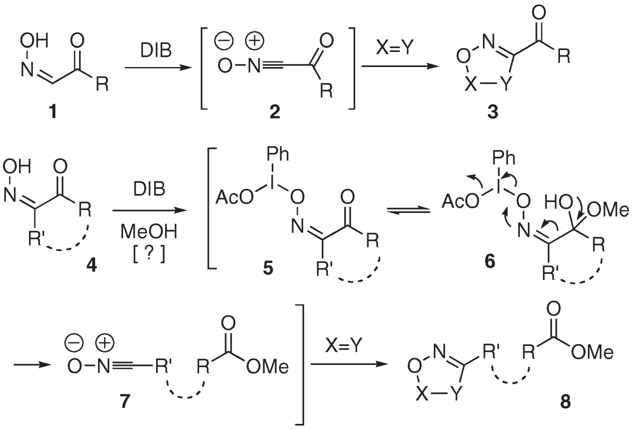


Upon reaction with PhI(OAc)$_2$, α-oxo-aldoximes are oxidized to α-oxo-nitrile oxides, while α-oxo-ketoximes are converted into nitrile oxides via the oxidative cleavage of the carbonyl–imino σ bond. The nitrile oxides thus formed were trapped with norbornene or styrene in good yield. α,α′-Dioxo-ketoximes react less efficiently.

A recent contribution from our laboratory[1] describes the oxidation of aldoximes to nitrile oxides with hypervalent iodine reagents[2] such as PhI(OAc)$_2$ ("DIB").[3] While the technique was initially developed with the aim of achieving a tandem phenolic oxidative amidation[4]–intramolecular nitrile oxide cycloaddition[5] sequence,[6] a wider range of applications may be envisioned. For instance, the oxidation of α-oxo-aldoxime **1** (Scheme 1), R = OEt, could lead to carbethoxyformonitrile oxide (CEFNO).[7] Alternatively, oxidative attack of α-oxo-ketoximes **4** in, e.g., MeOH could proceed with solvolytic fragmentation of the carbonyl-imino C–C bond, leading to the formation of nitrile oxides such as **7**. Products **3** and **8** ensuing from the reaction of such reactive 1,3-dipoles with appropriate dipolarophiles (cf. the generic species X = Y in Scheme 1), e.g., olefins, are generally useful in synthetic[8] and medicinal[9] chemistry.

SCHEME 1. Predicted Course of the DIB Oxidation of α-Oxo-Oximes



A screen of suitable conditions for the conduct of the desired transformation was carried out with oxime **9**[10] as a test substrate and norbornene as a trap for the nascent nitrile oxide. This exercise ascertained that, much as in the original case,[1] the reaction was best carried out in MeOH, at room temperature, in the presence of TFA (0.1–1% v/v; Table 1).

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[1] Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539.

[2] Reviews: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Kita, Y. *Yakugaku Zasshi* **2002**, *122*, 1011. (e) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. Monograph: (f) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 1997.

[3] Other methods for the oxidation of oximes to nitrile oxides with hypervalent iodine reagents: (a) Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 1625 (PhICl$_2$). (b) Tanaka, S.; Ito, M.; Kishikawa, K.; Kohmoto, S.; Yamamoto, M. *Nippon Kagaku Kaishi* **2002**, *3*, 471 (PhIO). (c) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Ravinder Reddy, M. *Tetrahedron Lett.* **2004**, *45*, 7347 (DIB). (d) Das, B.; Holla, H.; Maheder, G.; Venkateswarlu, K.; Bangdar, B. P. *Synthesis* **2005**, 1572 (DIB). (e) Chatterjee, N.; Pandit, P.; Halder, S.; Patra, A.; Maiti, D. K. *J. Org. Chem.* **2008**, *73*, 7775 (PhIO). (f) Raihan, M. J.; Kavala, V.; Kuo, C.-W.; Rama Raju, B.; Yao, C. F. *Green Chem.* **2010**, *12*, 1090 (PhI(OH)OTs). These techniques, however, are unsuitable for the conduct of tandem oxidative amidation/intramolecular nitrile oxide cycloaddition sequences (see text and ref 6).

[4] Reviews: (a) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (b) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759. Recent developments: (c) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (d) Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760. (e) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (f) Liang, H.; Ciufolini, M. A. *Chem.—Eur. J.* **2010**, *16*, 13262. See also: (g) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (h) Braun, N. A.; Bray, J.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985. (i) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E.-M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (j) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (k) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175.

[5] Reviews on intramolecular nitrile oxide cycloadditions: (a) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, Germany, 1990; Vol. I, p 77. (b) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. See especially pp 12255–12259.

[6] (a) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736. The methodology also enables the conduct of oxidative phenolic alkoxylation/INOC sequences: (b) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.

[7] Key references: (a) Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 731. (b) Panizzi, L. *Gazz. Chim. Ital.* **1939**, *69*, 332. (c) Vaughan, W. R.; Spencer, J. L. *J. Org. Chem.* **1960**, *25*, 1160. (d) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.

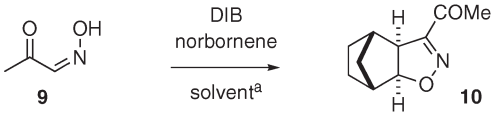
[8] Reviews on bimolecular nitrile oxide cycloadditions and synthetic applications thereof: (a) Grundmann, C. *Synthesis* **1970**, 344. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (c) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vols. 1 and 2. (d) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York. 1988. (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (f) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719. (g) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (h) Belen'kii, L. I. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: Hoboken, NJ, 2008; pp 1–128. See also ref 5.

[9] Bondar, N. F.; Isaenya, L. P.; Skupskaya, R. V.; Lakhvich, F. A. *Russ. J. Org. Chem.* **2003**, *39*, 1089.

[10] Commercially available.

DOI: 10.1021/jo102241s

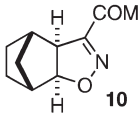
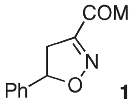
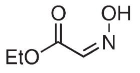
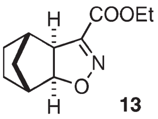
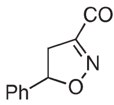
TABLE 1. Effect of Solvent, Temperature, and Reaction Time on the DIB Oxidation of α-Oximinoacetone[a]



entry	solvent	time	temp	yield[b]
a	CH$_3$CN	overnight	rt	30
b	CH$_3$CN/TFA(1%)	overnight	rt	26
c	MeOH	overnight	rt	74
d	MeOH/TFA(0.1%)	overnight	rt	76
e	MeOH/TFA (1%)	overnight	rt	75
f	MeOH/TFA(10%)	overnight	rt	0
g	MeOH/TFA (1%)	overnight	40 °C	52
h	MeOH/TFA (1%)	4.5 h	rt	67
i	MeOH/TFA (1%)	2 h	rt	69
j	MeOH/TFA (1%)	30 min	rt	74[c]

[a] Typical procedure: a solution of **9** (130 mg, 1.5 mmol) in a solvent (3 mL) was added slowly to a stirred solution of DIB (580 mg, 1.8 mmol, 1.2 equiv), TFA (table body), and norbornene (151 mg, 1.8 mmol, 1.2 equiv) in the same solvent (2 mL). Another 0.5 mL of solvent was used to transfer any remaining oxime into the solution. After the stated time, the mixture was evaporated in vacuo and the residue was purified by flash chromatography. We note that **10** is slightly volatile: to minimize loss of material, it should not be allowed to stand under vacuum (removal of traces of chromatographic eluants) for longer than necessary. [b] Yields of chromatographically purified product. [c] Such a short reaction time may be insufficient to promote complete oxidation of other oximes.

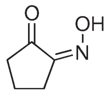
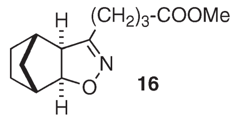
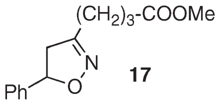
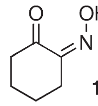
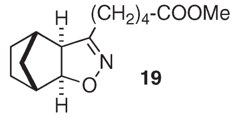
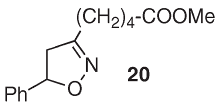
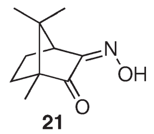
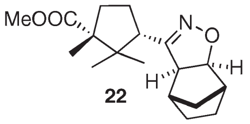
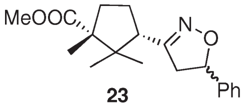
TABLE 2. DIB Oxidation of α-Oxo-Aldoximes 9 and 12[a]

entry	oxime	trap[b]	product	yield %[c]
a	**9**	N	 **10**	76
b	**9**	S	 **11**	75[d]
c	 **12**	N	 **13**	90
d	**12**	S	 **14**	82

[a] Typical procedure: a solution of oxime (1.5 mmol) in MeOH (3.5 mL total) was added slowly to a stirred solution of DIB (580 mg, 1.8 mmol, 1.2 equiv), TFA (55 μL, 1% v/v), and norbornene (151 mg, 1.8 mmol, 1.2 equiv) in the same solvent (2 mL). After the stated time, the mixture was evaporated in vacuo and the residue was purified by flash chromatography (see the Experimental Section for details). [b] N = norbornene; S = styrene. [c] Yields of chromatographically purified product. [d] This reaction was run with 0.1% v/v of TFA. A reaction run with the customary 1% TFA afforded **11** in only 59% yield.

In particular, higher temperatures or larger amounts of TFA (cf. entries f and g) had an adverse effect on the reaction.

TABLE 3. Oxidation of α-Oxo-Ketoximes[a]

entry	oxime	trap[b]	product	yield %[c]
a	 **15**	N	 **16**	70
b	**15**	S	 **17**	40
c	 **18**	N	 **19**	56[d]
d	**18**	S	 **20**	23[d]
e	 **21**	N	 **22**	72[e]
f	**21**	S	 **23**	24[f]

[a] All reactions run under the conditions of Table 2. [b] N = norbornene; S = styrene. [c] Yields of chromatographically purified product. [d] The yield of this reaction was unchanged when the amount of TFA was reduced to 0.1% (v/v). [e] The product was obtained as a 1:1 mixture of *exo* diastereomers arising from the two possible topologies of the cycloaddition step. [f] The product was obtained as a 1:0.8 mixture of unassigned Ph epimers.

The DIB oxidation of α-oxo-aldoximes **9**[10] and **12** under the foregoing conditions, and in the presence of norbornene or styrene as the olefinic trap, proceeded to afford products **10**−**11** and **13**−**14** in good yield (Table 2). Furthermore, the oxidative attack of α-oxo-ketoximes **15**,[11] **18**,[12] and **21**[13] with DIB in MeOH promoted nitrile oxide formation in concert with the anticipated C−C bond fragmentation. The expected norbornene-derived isoxazolines were isolated in good yield (Table 3). It should be noted that compounds of the type **16** have been used as building blocks for the synthesis of prostaglandin analogues.[9] Of special note is the conversion of (D)-camphor-derived **21** into a nearly 1:1 mixture of diastereomers of *exo*-adducts **22**, which clearly arose from the two possible *exo* topologies of the cycloaddition step. However, the reaction consistently afforded poorer yields when styrene was used as the trap. The reasons for this remain unclear at this time.

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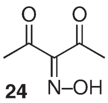
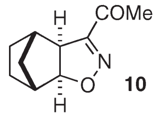
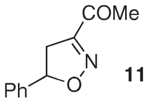
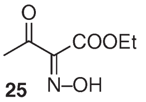
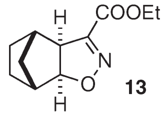
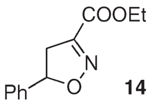
(11) Prepared according to: Cope, A. C.; Estes, L. L., Jr.; Emery, J. R.; Haven, A. C., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 1199.

(12) Prepared according to: Werber, F. X. US 19610919 (CAS No. 61:83839). Details are provided as Supporting Information.

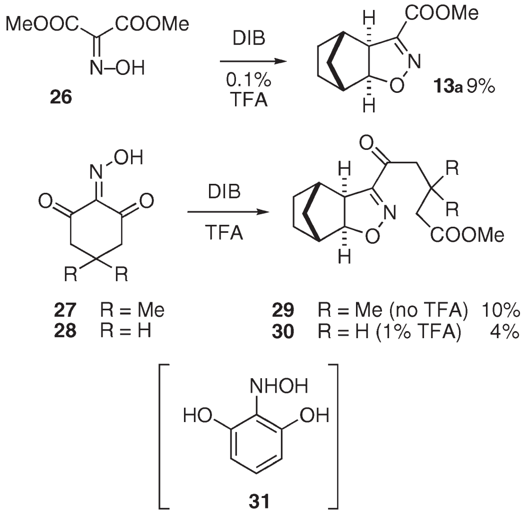
(13) Prepared according to: Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87.

TABLE 4. Oxidation of α,α′-Dioxo-Ketoximes in MeOH[a]

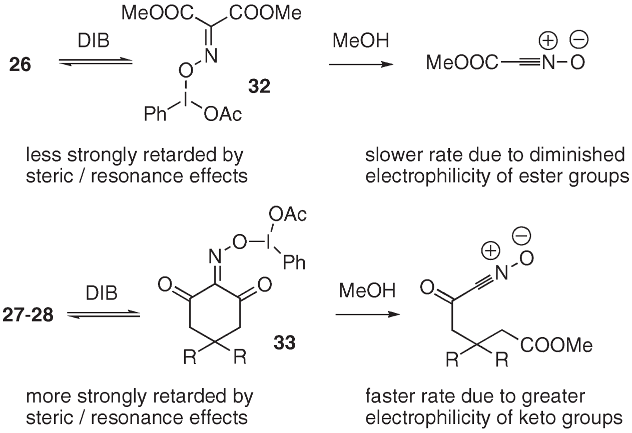
entry	oxime	trap[b]	product	yield %[c]
a	 **24**	N	 **10**	77[d]
b	**24**	S	 **11**	74[d]
c	 **25**	N	 **13**	52[e]
d	**25**	S	 **14**	59[f]

[a] The same procedure detailed in Table 2 was utilized in the present case. [b] N = norbornene; S = styrene. [c] Yields of chromatographically purified product. [d] Reaction run with 0.1% TFA. [e] Chromatography permitted the recovery of 29% of the starting oxime **25**. Also, the yield of **13** dropped to 19% with 0.1% TFA. [f] The yield of **14** dropped to 24% with 0.1% TFA.

SCHEME 2. Poor Substrates for the Reaction



SCHEME 3. Problematic Steps in the Reaction of Substrates 26–28



less strongly retarded by steric / resonance effects

slower rate due to diminished electrophilicity of ester groups

more strongly retarded by steric / resonance effects

faster rate due to greater electrophilicity of keto groups

Contrary to the foregoing oximes, α,α′-dioxo-ketoximes proved to be generally unsatisfactory substrates. As seen in Table 4, the DIB oxidation of **24**[14] proceeded as well as that of **9**, but the reaction of **25**[15] was less efficient than that of **12**. It should also be noted that when the oxidation of **25** was carried out in the less nucleophilic EtOH as the solvent, product **13** was isolated in 32% yield together with 30% recovered **25**, and **14** was obtained in 47% yield with 37% recovered **25**. By contrast, the reaction of oxime **12** to furnish **14**, a process that does not require a solvolytic step, proceeded equally well in EtOH (86% yield) and in MeOH (82% yield, Table 2), consistent with the assumption (Scheme 1) that nitrile oxide formation depends on the rate of solvolytic fragmentation of an intermediate such as **5**.

Substrates **26**,[16] **27**,[17] and **28**[17] (Scheme 2) were even more problematic. Thus, compound **13a** emerged in only 9% yield upon treatment of **26** with methanolic DIB/TFA and norbonene, while **29** was obtained in 10% yield from the reaction of **27** under similar conditions, but with no added TFA. Finally, DIB oxidation of compound **28** provided **30** in a meager 4% yield.[18] While the substrate clearly existed as the diketo-oxime tautomer (^{1}H and ^{13}C NMR), we cannot exclude formation of the aromatic tautomer **31** under the acidic conditions of the reaction. In all likelihood, such a highly electron-rich aromatic compound would be lost to oxidative polymerization in the presence of DIB. This could possibly account for the low yield.

At this time, however, we believe that the main factor responsible for the generally disappointing behavior of α,α′-dioxo-ketoximes is a severely retarded rate of formation and/or of nucleophilic cleavage of presumed intermediate of the type **5** (cf. **32**–**33**, Scheme 3). It seems likely that the pair of flanking carbonyls diminish the nucleophilicity of the OH group of the oxime by a combination of inductive, resonance, and steric effects. Steric barriers and mesomeric abatement of nucleophilicity may be especially pronounced in **33**, wherein conformational rigidity and near planarity of the dioxoketoxime system enhance resonance interactions and compress the OH group against a carbonyl system. On the other hand, the diminished electrophilic character of ester groups, relative to ketones, is likely to retard the solvolysis of species **32**, compounding the difficulty of converting ester substrates into a nitrile oxide. Such an explanation is consistent with the increasingly poorer yields of cycloadducts observed as the keto groups in oxime **24** are replaced with ester groups (cf. **25** vs **26**).

In summary, hypervalent iodine reagents such as DIB mediate the oxidative conversion of α-oxo-oximes into nitrile

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[14] Obtained as per: Cai, X.-H.; Yang, H.-J.; Zhang, G. L. *Synthesis* **2005**, 1569.

[15] Prepared according to: Rodionov, V. M.; Machinskaya, I. V.; Belikov, V. M. *Zh. Obshch. Khim.* **1948**, *18*, 917.

[16] Obtained as per: Hellmann, H.; Lingens, F. *Z. Phys. Chem.* **1954**, *297*, 283.

[17] Prepared according to: Zolfigol, M. A. *Molecules* **2001**, *6*, 694.

[18] Because of such poor yields, compounds **29** and **30** were not fully characterized.

oxides in a generally satisfactory manner, while α,α′-dioxo-oximes are generally poor substrates for the reaction. The method complements existing avenues to analogous nitrile oxides,[19] the usefulness of which is likely to make this chemistry of interest to a broad cross section of synthetic and medicinal chemists.

Experimental Section[20]

General Procedure for the Oxidation of α-Oxo-Aldoximes: Preparation of Compound 13. A solution of oxime **12** (158 mg, 77% w/w in toluene, 1.04 mmol) in MeOH (2 mL) was added over 20 min to a well-stirred solution of DIB (402 mg, 1.25 mmol, 1.2 equiv), TFA (70 μL, 1% v/v), and norbornene (117 mg, 1.25 mmol, 1.2 equiv) in MeOH (4.5 mL) at rt (the solution became homogeneous after addition of TFA). An additional 0.5 mL of MeOH was used to transfer residual oxime into the reaction mixture. A series of color changes, from colorless to light yellow, occurred. After stirring for 30 min at rt, the mixture was evaporated in vacuo and the residue was purified by flash chromatography (step gradient 5%, 10%, 15%, and 20% EtOAc/hexane) to afford 194 mg (90% yield) of the known **13**[19] as a clear, viscous oil. ^{1}H NMR 4.65 (br d, 1H, J = 8.5 Hz), 4.31 (m, 2H), 3.27 (br d, 1H, J = 8.5 Hz), 2.57 (br d, 2H, J = 10.0 Hz), 1.54 (m, 2H), 1.37 (m, 1H), 1.34 (t, 3H, J = 7.1 Hz), 1.23 (m, 2H), 1.11 (m, 1H). ^{13}C NMR 160.9, 152.3, 90.3, 61.9, 55.7, 43.0, 39.4, 32.3, 27.2, 22.7, 14.2. ESI-MS [M + Na]$^+$ 232.3. HRMS calcd for $C_{11}H_{15}NO_3Na$ 232.0950, found 232.0948.

General Procedure for the Oxidation of α-Oxo-Ketoximes: Preparation of Compound 16. A solution of oxime **15** (50 mg, 0.44 mmol) in MeOH (3 mL) was added dropwise at rt to a solution of norbornene (50 mg, 1.2 equiv), PhI(OAc)$_2$ (170 mg, 1.2 equiv), TFA (1% v/v, 55 μL), and MeOH (2 mL) with stirring. Another 0.5 mL of MeOH was used to transfer any remaining oxime into the solution. The reaction was complete in 30 min. The crude product was purified by flash column chromatography by using a step-gradient (5%, 10%, 15%, and 20% ethyl acetate/hexane), and pure fractions were collected and concentrated in vacuo, yielding 74 mg (70%) of **16** as a colorless viscous oil. ^{1}H NMR 4.34 (d, 1H, J = 8.2 Hz), 3.61 (s, 3H), 2.95 (d, 1H, J = 8.2 Hz), 2.44 (br s, 1H), 2.40−2.12 (m, 5H), 2.00−1.76 (m, 2H), 1.56−1.29 (m, 3H), 1.22−0.96 (m, 3H). ^{13}C NMR 173.5, 157.9, 86.1, 59.3, 51.5, 42.8, 38.2, 33.2, 32.1, 27.2, 26.0, 22.7, 21.4. IR 1732. ESI-MS [M + Na]$^+$ 260.4. HRMS calcd for $C_{13}H_{19}NO_3Na$ 260.1263, found 260.1265.

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Supporting Information Available: experimental protocols, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) E.g.: (a) Cecchi, L.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852. (b) Machetti, F.; Cecchi, L.; Trogu, E.; De Sarlo, F. *Eur. J. Org. Chem.* **2007**, 4352 and references cited therein.

(20) Experimental protocols are provided as Supporting Information.