Chemistry of Heterocyclic Compounds, Vol. 46, No. 10, 2011

COMPARATIVE STUDY OF THE DIFFERENT APPROACHES TO THE SYNTHESIS OF ISATINS WITH A CHIRAL SUBSTITUENT AT THE NITROGEN ATOM

A. V. Kurkin[1]*, A. A. Bernovskaya[1], and M. A. Yurovskaya[1]

Through a comparative study of three different routes to the synthesis of isatins with a chiral substituent on the nitrogen atom it has been shown that better results for preparing the isatins are achieved using the Sandmeyer (>99% ee, yield 50%) rather than the Stolle method (95% ee, yield 16%). The procedure proposed by Gassman for preparing isatins was unsuitable for the compounds described.

Keywords: chiral N-arylanilines, isatins with a chiral substituent on the nitrogen atom, the Sandmeyer, Stolle, and Gassman methods, enantioselectivity.

Isatin and its derivatives are widely used in the synthesis of a broad range of heterocyclic compounds and they are also as starting material for preparing drugs. The interest in isatin derivatives is due to their broad spectrum of biological activity They show antimicrobial and antiviral activity, affect the CNS, are involved in metabolism, and stimulate plant growth [1].

The preparation of novel isatins, a study of their properties, and their use as building blocks for the synthesis of other heterocyclic structures are interesting and timely questions. This especially concerns isatin derivatives with a chiral substituent on the nitrogen atom, evidence for which is absent in the literature. The importance of problem of the synthesis of chiral derivatives is due to the fact that, among substances synthesized every year and undergoing biological testing, ever more attention is paid to enantiomerically pure (not racemic) compounds and these substances are increasingly used as drugs [2].

Several basic routes to the synthesis of isatins with an alkyl or aryl substituent on the nitrogen atom can be identified [3]. The first of these is the preparation of isatins developed by Sandmeyer. It is based on the reaction of aromatic amines with chloral hydrate and hydroxylamine hydrochloride to give isonitrosoacetanilides. In the presence of sulfuric acid they cyclize to the corresponding isatins. In the Sandmeyer reaction it is possible to use anilines containing electron acceptor groups in the aromatic ring and heterocyclic amines [1]. The reaction is simple in use, the starting materials are cheap, and the cyclization product yields often exceed 75% [1] hence this route is widely used in practice. However, the yields depend on the structure of the starting amine, e.g. in the cyclization of 5-methylaniline to the isatin the yield amounts to only 22% [3]. One of the important alternatives to the Sandmeyer method is that for preparing isatins due to Stolle. In this, aniline

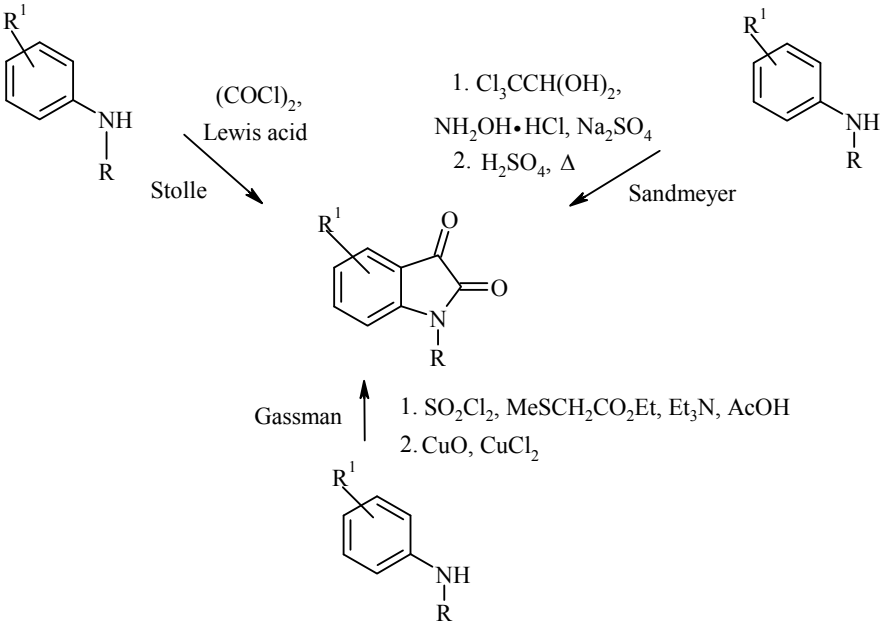
*To whom correspondence should be addressed, e-mail: kurkin@direction.chem.msu.ru.

[1]M. V. Lomonosov State University, Moscow 119991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1497-1504, October, 2010. Original article submitted June 8, 2010.

derivatives react with excess oxalyl chloride to give intermediate N-aryloxanilic acid chlorides which cyclize to isatins in the presence of Lewis acids [1]. It should be noted that Stolle reaction yields are typically in the range 30-60% and substrates containing electron acceptor groups do not take part. A third method for preparing both unsubstituted and N-alkyl-substituted isatins is the Gassman reaction. From an aniline derivative it produces an intermediate 3-methylthio-2-oxindole which is oxidized to the corresponding isatin, e.g. using $NaIO_4$ in THF. The cyclization product yields in the Gassman reaction range from 40 to 80% but, with the presence in the substrate structure of a readily oxidizable group (e.g. hydroxyl or aldehyde), this method loses its attraction [3].

As follows from the above, the majority of the widely used practical methods for preparing isatin derivatives from anilines can be successfully used for obtaining N-alkylated isatins. Hence anilines which contain a chiral substituent on the nitrogen can be involved in different cyclizations to give isatins. In this work we have carried out a comparative study of the efficiency and stereoselectivity of the three different routes for preparing isatins with a chiral substituent on the nitrogen through the Sandmeyer, Stolle, and Gassman approaches.

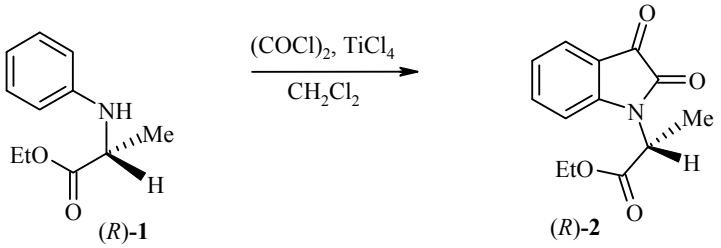


R = H, Alk; R^1 = H, Hal, Alk, OAlk

As starting materials for the preparation of the isatins with a chiral substituent on the nitrogen atom we selected optically active N-arylalanines. They were synthesized under stereospecific conditions using the Mitsunobu reaction by alkylation of N-arylsulfonylanilines with the commercially available ethyl (*S*)-lactate. We have previously reported the potential preparation of such optically active N-arylalanines in good yields and with high enantioselectivity (>99% *ee*) as well as the cyclization of these chiral anilines to isatins using the Sandmeyer method [4]. The enantiomeric purity of the isatins prepared was determined by HPLC using a chiral stationary phase as 97-99% *ee* with a yield of 52-67%. Because varying the substituent in the benzene ring of the aniline (H, Br, Me) did not affect the reaction course we decide to select two approaches to the synthesis of the racemic and enantiomerically pure (*R*)-isomer of ethyl N-(4-phenylamino)propionate as model substrates. We selected and developed conditions for the racemic substrate which were then used for its enantiomerically pure analog in order to study the enantioselectivity of the reaction.

A similar strategy was also used for studying the applicability of the Stolle method for preparing isatins with a chiral substituent on the nitrogen atom.

In the Stolle synthesis of isatins it is known that N-aryloxanilic acid chlorides (prepared by condensation of anilines with excess oxalyl chloride) cyclize to the corresponding isatins in the presence of different Lewis acids, *viz*. $AlCl_3$ [5], $BF_3 \cdot Et_2O$ [6], or $TiCl_4$ [7]. The reaction is often carried out by heating with carbon disulfide, methylene chloride, tetrachloroethane, benzene, or chloroform used as solvent [1]. We wanted to select that synthetic method for isatins with a chiral substituent at the nitrogen atom which would take place under the mildest conditions and would not lead to the racemization of optically active substrates. We chose the method reported in the literature in which $TiCl_4$ was used as Lewis acid and methylene chloride at 12ºC used as solvent [7]. However, in these conditions, we were unable to observe formation of the target isatin and separated only the starting amine **1**. Change in the conditions (amount of $TiCl_4$, reaction time, temperature) led to improved results. The highest yield of isatin (58%) was achieved by heating the reaction mixture at 30-35ºC for 6 h (Table 1).



Thus having optimized the Stolle method of synthesizing isatins for the racemic N-alkylated amine we extended it to the enantiomerically pure analog. An important feature of our study is the question of the retention of the optical purity of the isatin prepared with a chiral substituent on the nitrogen atom. We carried out the experiments numbered 2, 4, and 5 to reveal how the reaction time and temperature influenced the isatin enantiomer yield. It was found that an increase in temperature affected the retention of isatin optical purity to a lesser extent than an increase in the reaction time to 6 days. The highest enantiomeric purity for the isatin (*R*)-**2** was achieved in experiment 2 (24 h, ~ 20ºC) with 95% *ee*, i.e. partial racemization was observed even here. The angles of rotation were measured for the isatins obtained by the three experimental routes (Table 2).

TABLE 1. Optimization of the Stolle Cyclization Conditions*

Experiment	$TiCl_4$, equiv.	Reaction conditions		Yield of isatine, %
		T, °C	Time, h	
1	4	12	16 [7]	—
2	4	20	24	14
3	6	20	24	32
4	4	20	144 (6 days)	55
5	4	30-35	6	58

* The conditions were developed for the racemic compounds.

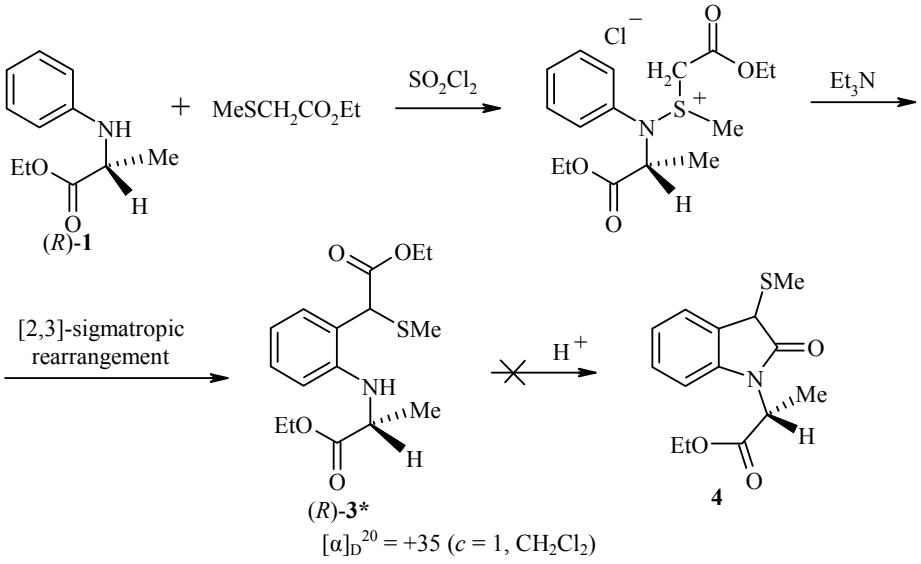
TABLE 2. Characteristics of the Isatins with a Chiral Substituent on the Nitrogen Atom

Experiment	Enantiomeric purity of the chiral isatin, % *ee*	$[\alpha]_D^{20}$ of the isatin, c = 1 g/100 ml dichloromethane	Isatin yield, %
2	95	+18	16
4	73	+16	38

The Gassman synthesis is another variant of the cyclization of an N-alkylated amine to the isatin. In this case there occurs the formation and subsequent oxidation of an intermediate 3-methylsulfanyl-2-oxindole [8] whose synthesis can involve two methods depending on the electronic effects of the substituent in the aromatic ring. In the case of electron acceptor groups the oxindole derivative is prepared from the intermediate N-chloroaniline which reacts with ethyl methylthioaceate to form an azosulfonium salt [9]. For electron donor substituents (which destabilize the N-chloro intermediate and hence lower the yields of the azosulfonium salt) a second method is used involving reaction of a chlorosulfonium salt with the corresponding aniline [10].

The intermediate 3-methylsulfanyl-2-oxindole is then oxidized to the isatin by several methods, e.g. by carrying out a reaction with N-chlorosuccinimide to yield the unstable 3-chloro-3-methylsulfanyl-2-oxoindoles which are hydrolyzed to isatins in the presence of mercuric oxide and boron trifluoride etherate in aqueous THF [8]. It is possible to obtain the isatins by oxidation of the oxindole derivatives with a mixture of copper(II) oxide and chloride [7].

We have used two routes to the Gassman synthesis of isatins, *viz.* its modification in which the chlorosulfonium salt is prepared from the corresponding sulfoxide and oxalyl chloride [11] and the classical variant. In the first case we could not prepare the target compound and only the starting amine **1** was isolated from the reaction mixture. In the second case the reaction did not go to completion and LCMS data showed that the reaction mixture contained the acyclic intermediate compound **3** as well as the starting amine **1**.



* We have proposed an (*R*)-configuration for compound **3** because the chiral center is not affected in the reaction process. A separate study to establish the absolute configuration has not been carried out.

Increasing the reaction time and the amount of the reagents led only to lowering of the yields of the acyclic intermediate compound **3** (Table 3)

TABLE 3. Optimization of the Conditions for Preparing the Acyclic Compound **3***

Experiment	SO_2Cl_2 ($MeSCH_2CO_2Et$) and Et_3N, equiv.	Reaction time, h	Yield of compound **3**, %
1	1.06 and 1.04	3.5	27
2	1.5 and 1.47	3.5	18
3	1.06 and 1.04	5.5	13

* The conditions were developed for the racemic compounds.

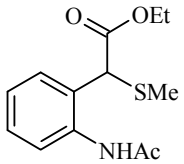
TABLE 4. Selection of Conditions for Compound **3** Cyclization*

Experiment	H^+	Reaction conditions	
		T, °C	Time, h
1	AcOH [7]	20	1
2	CF_3COOH	20	24
3	2 mol/l HCl [11]	20	18
4	6 mol/l HCl	20	24
5	12 mol/l HCl	20	24
6	1 mol/l HCl [5]	65	2
7	6 mol/l HCl	65	4.5
8	12 mol/l HCl	78	2

* The cyclization product **4** was not seen in any of the experiments.

We considered that the reason for the lack of success is an insufficient medium acidity. However, the use of the stronger trifluoroacetic and hydrochloric acids at different concentrations (Table 4) also did not yield the cyclization product **4**.

From LCMS data we observed the starting amine **3** as well as its hydrolysis product in the reaction mixture. It is possible that we were unable to prepare the cyclization product **4** because of steric hindrances. In [9] the authors reported the preparation of stable *o*-aminophenylacetic acid derivatives, one example of which is compound **5**. This was separated and fully characterized but attempts to cyclize it to the corresponding 3-methylthio-2-oxindole were not undertaken by the authors.



5

In the case of the enantiomerically pure amine (*R*)-**1** as starting material in the Gassman synthesis we also observed the formation of compound **3** which showed optical activity and whose angle of rotation was measured.

Hence the Sandmeyer and Stolle methods of the three proposed by us as routes to isatins with a chiral substituent on the nitrtogen atom led to the target isatins. The Gassman synthesis proved to be unsuited to our model substrate. In the case of the optically active isatins prepared according to Sandmeyer we achieved better results (>99% *ee*, yield >50%) than for those compounds using the Stolle method (95% *ee* with a yield of 16%).

EXPERIMENTAL

IR spectra were recorded on a Thermal Nicolet IR200 FT instrument and ^1H and ^{13}C NMR spectra on a Bruker AMX-400 (400 ad 100 MHz respectively) using $CDCl_3$ with TMS as internal standard. Chromato-mass spectrometry was carried out using a Carlo Erba/Kratos Fractovap Series 4200 gas liquid chromatograph with a Hewlett Packard Ultra-1 column (25 m×0.2 mm, phase layer thickness 0.33 μm, helium gas carrier at 1 ml/min, flow split 1:10, evaporator temperature 280ºC, and temperature gradient from 150 to 280ºC at 5ºC/min). IDT-700 mass spectrometric detector (Finnigan MAT), EI mode, ionization energy 70 eV, mass range *m/z* 45-400. The

specific rotation was measured on a Jasco DIP-360 (589 nm) polarimeter. Monitoring of the reaction course and the purity of the separated compounds were carried out by TLC on Silufol UV-254 plates. The determination of enantiomeric purity was carried out by HPLC using a Chiralpak AD-RH stationary phase (4.6×150 mm, 5 μm, eluent H_2O + CF_3COOH/MeCN (50:50), 1.0 ml/min flow rate, ~ 20ºC, 250 nm).

Stolle Synthesis of the Isatins (Table 1).

Experiment No. 2. A solution of ethyl 3-phenylaminopropionate (0.5 g, 2.59 mmol) in dichloromethane (3 ml) was added dropwise with stirring to a cooled (0ºC) solution of oxalyl chloride (0.35 ml, 4.19 mmol) in dichloromethane (1 ml). The reaction mixture was stirred at room temperature for 2 h and the solvent was evaporated *in vacuo*. The residue obtained was dissolved in dichloromethane (3 ml) and treated with $TiCl_4$ (1 molar dichloromethane solution, 1.13 ml, 0.01 mol). The reaction mixture was stirred at room temperature for 24 h, poured into ice, extracted with dichloromethane (3×5 ml), dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was flash chromatographed using dichloromethane.

Experiment No. 3. Similar to experiment No. 2 but using 6 equivalents of $TiCl_4$ in place of 4 equivalents.

Experiment No. 4. Similar to experiment No. 2 but with stirring of the reaction mixture for 144 h (6 days).

Experiment No. 5. Similar to experiment No. 2 but with stirring of the reaction mixture for 6 h at 30-35ºC.

Ethyl 2-(Isatin-1-yl)propionate (2). Yield 14% (experiment No. 2), 32% (No. 3), 55% (No. 4), 58% (No. 5); mp 69ºC (a mixture of petroleum ether and ethyl acetate). IR spectrum, ν, cm^{-1}: 3467, 2993, 1739 (CO), 1608, 1468, 1367, 1309, 1246, 1113, 750, 476. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 1.69 (3H, d, *J* = 7.5, $CHC\underline{H}_3$); 4.18-4.27 (2H, m, $C\underline{H}_2CH_3$); 5.16 (1H, q, *J* = 7.5, $C\underline{H}CH_3$); 6.85 (1H, br. d, *J* = 7.7, CH Ar); 7.15 (1H, ddd, *J* = 7.7, *J* = 7.7, *J* = 0.7, CH Ar); 7.57 (1H, ddd, *J* = 7.7, *J* = 7.7, *J* = 1.4, CH Ar); 7.65 (1H, ddd, *J* = 7.7, *J* = 1.4, *J* = 0.7, CH Ar). ^{13}C NMR spectrum, δ, ppm: 14.08 (CH_3); 14.27 (CH_3); 49.18 (CH); 62.16 (CH_2); 111.46 (CH); 117.89 (C); 123.89 (CH), 125.64 (CH); 138.19 (CH); 149.45 (C); 157.69 (CO); 169.43 (CO); 182.70 (CO). Mass spectrum, *m/z* (I_{rel}, %): 247 $[M]^+$ (11), 174 $[M^+ - CO_2Et]$ (8), 146 $[M^+ - MeCHCO_2Et]$ (100), 128 (0.8), 117 (6), 91 (12), 77 (26), 51 (9). Found, %: C 63.20; H 5.43; N 5.81. $C_{13}H_{13}NO_4$. Calculated, %: C 63.15; H 5.30; N 5.66.

(*R*)-Ethyl 2-(Isatin-1-yl)propionate ((*R*)-2) (see Table 2).

Gassman Synthesis of Isatins (Table 3).

Experiment No. 1. Sulfuryl chloride (0.22 ml, 2.74 mmol) was added dropwise with stirring to a cooled (-78ºC) solution of methyl methylthioacetate (0.35 ml, 2.74 mmol) in dichloromethane (26 ml) and stirred for 20 min. A solution of ethyl N-(4-phenylamino)propionate (0.5 g, 2.59 mmol) and 1,8-bis(dimethyl-amino)naphthalene (0.58 g, 2.69 mmol) in dichloromethane (16 ml) was added, stirred for 3.5 h at -78ºC, triethylamine (0.38 ml, 2.69 mmol) was added, and the product was stirred at -78ºC for a further 15 min and then for 20 h at room temperature. Acetic acid (2.6 ml) was added and the product was stirred for 1 h at room temperature. The reaction mixture was washed with water, saturated NaCl solution, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was chromatographed on a wet silica gel column eluting with a mixture of petroleum ether and ethyl acetate (10:1).

Experiment No. 2. Similar to experiment No.1 using 1.5 and 1.47 equivalents of SO_2Cl_2, ($MeSCH_2CO_2Et$), and Et_3N respectively instead of 1.06 and 1.04 equivalents.

Experiment No. 3. Similar to experiment No. 1 with the reaction mixture stirred for 5.5 h at -78ºC.

Ethyl 2-[2-(Ethoxycarbonylmethylsulfanylmethyl)phenylamino]propionate (3). Yield 27% (experiment No. 1), 18% (No. 2), 13% (method B). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (6H, t, *J* = 7.1, $2CH_2C\underline{H}_3$); 1.48 (3H, d, *J* = 6.7, $CHC\underline{H}_3$); 2.07 (3H, s, SCH_3); 4.08-4.30 (5H, m, $2C\underline{H}_2CH_3$, $C\underline{H}CH_3$); 4.42 (1H, s, $C\underline{H}SCH_3$); 6.58 (2H, d, *J* = 8.2, CH Ar); 7.28 (2H, d, *J* = 8.2, CH Ar). ^{13}C NMR spectrum, δ, ppm: 14.13 (CH_3); 14.18 (CH_3); 14.86 (CH_3); 14.86 (CH_3); 18.90 (CH_3); 51.88 (CH); 53.07 (CH); 61.20 (CH_2); 61.43 (CH_2); 113.25 (2C

CH); 124.91 (C); 129.53 (2C, CH); 146.42 (C); 171.08 (CO); 174.41 (CO). Mass spectrum, *m/z* (I_{rel}, %): 325 $[M]^+$ (9), 278 (100), 252 (42), 224 (6), 206 (19), 178 (25), 164 (32), 133 (55), 120 (16), 89 (22), 45 (17). Found, %: C 59.01; H 7.30; N 4.10. $C_{16}H_{23}NO_4S$. Calculated, %: C 59.05; H 7.12; N 4.30.

(*R*)-Ethyl 2-[2-(Ethoxycarbonylmethylsulfanylmethyl)phenylamino]propionate (3). $[\alpha]_D^{20}$ = +35 (*c* = 1, dichloromethane), yield 30% (experiment No. 1). The ^{1}H NMR and ^{13}C NMR spectra are identical to those of the racemic sample.

REFERENCES

1. G. I. Zhungietu and M. A. Rekhter, *Isatins and its Derivatives* [in Russian], Shtiintsa, Kishinev (1977).
2. V. Farinam, J. T. Reeves, C. H. Senanayake, and J. J. Song, *Chem. Rev.*, **106**, 2734 (2006).
3. J. F. Silva, S. J. Garden, and A. C. Pinto, *J. Braz. Chem. Soc.*, **12**, 273 (2001).
4. A. V. Kurkin, A. A. Bernovskaya, and M. A. Yurovskaya, *Tetrahedron Asymmetry*, **20**, 1500 (2009).
5. W. J. Welstead, Jr., H. W. Moran, H. F. Stauffer, L. B. Turnbull, and L. F. Sancilio, *J. Med. Chem.*, **22**, 1074 (1979).
6. G. Loloiu and O. Maior, *Rev. Roum. Chim.*, **42**, 67 (1997).
7. Y. Fukuda, Y. Itoh, K. Nakatani, and S. Terashima, *Tetrahedron*, **50**, 2793 (1994).
8. P. G. Gassman, J. Cue, and T. Y. Luh, *J. Org. Chem.*, **42**, 1344 (1977).
9. P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974).
10. P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).
11. S. W. Wright, L. D. McClure, and D. L. Hageman, *Tetrahedron Lett.*, **37**, 4631 (1996).