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Enantioselective Syntheses of Colletodiol, Colletol, and Grahamimycin A

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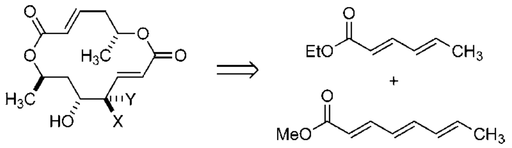
ABSTRACT



X=OH, Y=H, Colletodiol
X=H, Y=H, Colletol
X=O, Y=O, Grahamimycin A

The enantioselective synthesis of colletodiol has been achieved in 11 steps from methyl 1,3,5-octatrienoate and 16 total steps from both ethyl sorbate and methyl 1,3,5-octatrienoate. The route relies upon an enantio- and regioselective Sharpless dihydroxylation and a palladium-catalyzed reduction to form a 5-hydroxy-1-enoate and an 7-hydroxy-1,3-dienoate. These esters were further functionalized, coupled, and macrolactonized to provide colletodiol after deprotection. Grahamimycin A and colletol were synthesized in one and two steps, respectively, from colletodiol.

Colletodiol (**1**) is a 14-membered bis-macrolactone, which was isolated as a metabolite of the plant fungi *Colletotrichum capsici* and *Chaetomium funicola* in 1966[1] and 1969,[2] respectively. In 1968, MacMillan isolated and proposed structures for three other 14-membered bis-macrolactones from *C. capsici* metabolites colletol **2**, colletoallol **3**, and colletoketol **4** (Figure 1).[3] More recently, two related 14-membered bis-lactones were isolated from the aerobic fermentation of cultures of *Cytospora* sp. ATCC 20502, these being the structurally isomeric grahamimycin A **4** and grahamimycin A$_1$ **5**.[4] It was later realized that the structures of colletoketol and grahamimycin A were identical.[5]

While colletodiol **1** exhibits only mild antibiotic activity, grahamimycin A **4** (colletoketol) and grahamimycin A$_1$ **5** have shown significant activity against various pathogenic microorganisms. In particular, grahamimycin A **4** exhibited potent activity against several species of bacteria, blue-green algae, green algae, and five fungi. The absolute and relative stereochemistry of grahamimycin A$_1$ **5** was established by a combination of X-ray crystalography and total synthesis of the enantiomer from tartaric acid.[6] Similarly, the absolute and relative stereochemistry of colletodiol **1** was established via total synthesis by both Seebach and Mitsunobu, although both routes suffered from low yields of macrolactonization. The macrolactonization problems for colletodiol **1** and

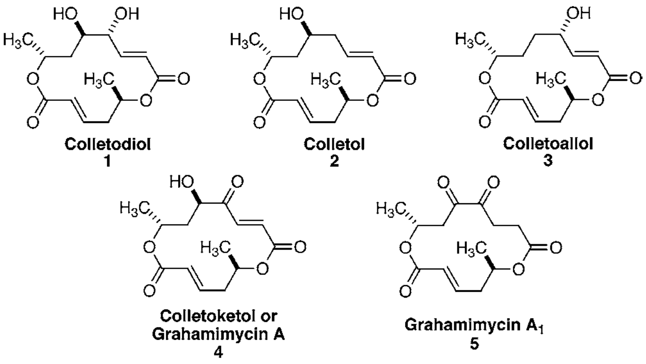


Figure 1.

[†] University of Minnesota.

(1) Grove, J. F.; Speake, R. N.; Ward, G. *J. Chem. Soc. C* **1966**, 230.

(2) Powell, J. W.; Whalley, W. B. *J. Chem. Soc. C* **1969**, 911.

(3) (a) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497. (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487−1493.

(4) Gurusiddaiah, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153−165.

(5) (a) O'Neill, J. A.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 738−740. (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896−906.

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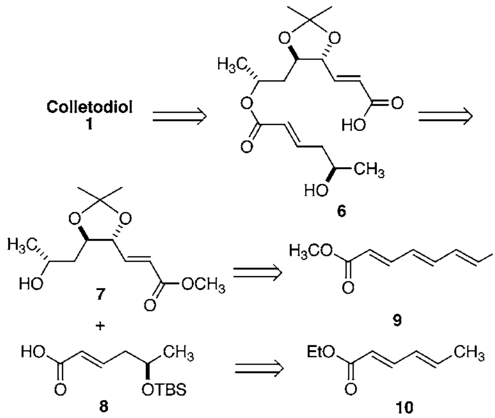
colletol **2** were skirted by Keck's use of DCC/DMAP[5b,7] conditions or by Kobayashi's use of Yamaguchi conditions.[8]

There have been several synthetic efforts toward colletodiol **1**,[9] colletol **2**,[10] and grahamimycin A$_1$ **5**.[11] Surprisingly, there has been only one route to the most biologically active structure, grahamimycin A (colletoketol) **4**, by Kobayashi,[8] who also reconfirmed its stereoselective conversion into colletodiol with NaBH$_4$. This reduction was first reported by Simpson[5a] and Ronald,[4] although a procedure was not reported.

As part of our efforts for the use of asymmetric catalysis for the enantioselective synthesis of antimicrobial lactones, we were interested in an enantioselective synthesis of colletodiol **1**. We targeted colletodiol because of its intermediary oxidation state; thus, we thought **1** would be a convenient precursor to the reduced isomers colletol **2** and colletoallol **3**, as well as the oxidized isomers grahamimycin A **4** and grahamimycin A$_1$ **5**. We were additionally interested in colletodiol because we thought it was an ideal substrate to test our catalytic Os/Pd-oxidation/reduction approach to 1,2- and 1,3-diols.[12]

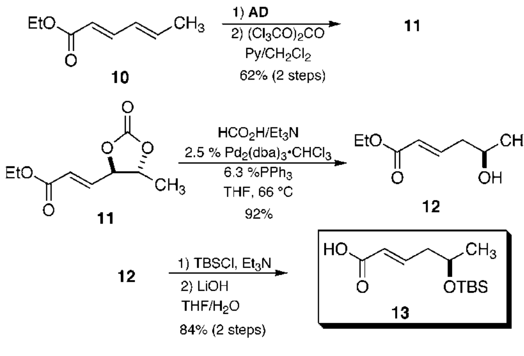
Scheme 1



Similar to the approaches of others, our retrosynthetic analysis of colletodiol envisioned a macrolactonization of hydroxyacid **6**, which could be prepared from an esterification coupling of alcohol **7** and hexenoic acid **8**. Our retrosynthetic plan diverges from others in our desire to establish the absolute and relative stereochemistry of colletodiol by a series of selective dihydroxylation reactions.[13] Thus, sequential application of our catalytic Os/Pd-oxidation/reduction sequence on methyl octa-1,2,3-trienoic acid **9** should allow for the installation of the triol stereochemistry of hydroxyester **7**. A similar approach should allow for the preparation of the hexenoic acid **8** from ethyl sorbate **10** (Scheme 1).

Following our reported protocol,[12] the commercially available ethyl sorbate **10**[14] was converted into alcohol **12** in three steps and a 57% overall yield (Scheme 2). The Sharpless dihydroxylation of ethyl sorbate **10** using (DHQD)$_2$–PHAL yielded the 4,5-diol in good yield (71%) and enantiomeric excess (>90%).[15,16] The diol hydroxyl groups were readily differentiated by taking advantage of π-allyl palladium chemistry.[17] The diol was converted into cyclic carbonate **11** by treating a CH$_2$Cl$_2$/pyridine solution of the diol with triphosgene (87%). Treatment of **11** with a catalytic amount of palladium and triphenylphosphine (2.5% Pd$_2$(dba)$_3$·CHCl$_3$/6.3% PPh$_3$)[18] and a mild hydride source (Et$_3$N/HCO$_2$H) afforded an excellent yield (92%) of the desired δ-hydroxyester **12**. The synthesis of the hexenoic acid fragment **13** was completed by first protection of the hydroxyl group as the TBS-ether (TBSCl/Et$_3$N, 96%) followed by ester hydrolysis (LiOH, 88%).

Scheme 2



AD = 1% OsO$_4$1.1% (DHQD)$_2$PHAL, 3 eq. K$_3$FeCN$_6$/ 3 eq. K$_2$CO$_3$/1 eq. MeSO$_2$NH$_2$ in 1:1 *t*-BuOH/H$_2$O, 0 °C

With the TBS-protected hydroxy acid **13** in hand, we next investigated the viability of this Os/Pd approach for the enantioselective conversion of trienoate **9** to the 7-hydroxy dienoate **16** by an identical three-step reaction sequence.

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(6) Seidel, W.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 159–162.

(7) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606–6611.

(8) Kobayashi, Y. Matsuumi, M. *J. Org. Chem.* **2000**, *65*, 7221–7224.

(9) For the synthesis of colletodiol, see refs 5 and 8 and: (a) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2159–2162. (b) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2163-2166. (c) Schnurrenberger, P.; Hungerbuhler, E.; Seebach, D. *Liebigs Ann. Chem.* **1987**, 733–744. (d) Fujiji, M.; Omura, T.; Furuyama, M.-A. Shimizu, I. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1997**, 376–371.

(10) For the synthesis of colletol, see the work of Keck et al., ref 7, and: (a) Shimizu, I.; Omura, T. *Chem. Lett.* **1993**, 1759–1760. (b) Sharma, G. V. M.; Raja Rao, A. V. S.; Murthy, V. S. *Tetrahedron Lett.* **1995**, *36*, 4117–4120. (c) Sollaoie, G.; Gressot, L. Colobert, F. *Eur. J. Org. Chem.* **2000**, 357–364.

(11) For the synthesis of grahamimycin A$_1$, see ref 6 and: (a) Ghiringhelli, D. *Tetrahedron Lett.* **1983**, *24*, 287–290. (b) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470–473. (c) Bestmann, H.-J.; Schobert, R. *Tetrahedron Lett.* **1987**, *28*, 6587–6590. (d) Ohta, K.; Miyagawa, O.; Tsutsui, H.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 523–535.

(12) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049–1052. (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780. (c) Garaas, S.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685.

(13) For a related but less efficient approach using the Sharpless epoxidation, see refs 9d and 10a.

(14) The Aldrich Chemical Co. sells ethyl sorbate for $0.30/g.

(15) All levels of enantioinduction were determined by HPLC analysis (8% IPA/Hexane, Chiralcel OD) and/or Mosher ester analysis. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

(16) All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR and HRMS.

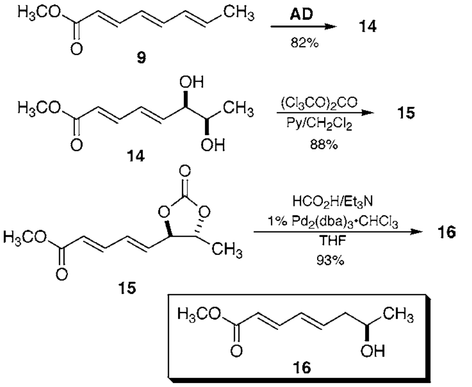
(17) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107–110.

(18) This lower than normal (2/1 phosphine to palladium) ratio gave higher yields and faster reaction times, whereas the use of ligandless conditions lead to the hydrogenation of the C–C double bond.

While Sharpless has shown the AD-mix reagent system selectively oxidizes triene **9** to diol **14** with no over oxidation,[19] we were concerned with the possibility of forming regioisomers and/or double-bond isomers during the palladium reaction.

Treatment of triene **9** with asymmetric dihydroxylation conditions gave diol **14** in an excellent yield (82%) and enantiomer excess (95% ee).[15,19,20] The cyclic carbonate was prepared by treating a CH_2Cl_2/pyridine solution of diol **14** with triphosgene, providing **15** in an 88% yield (Scheme 3).

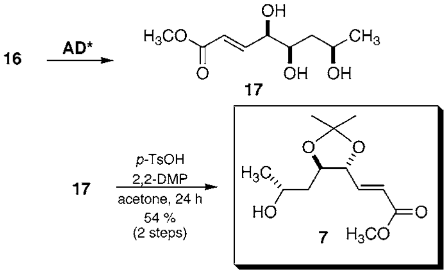
Scheme 3



AD = 1% $OsO_4$1.1% $(DHQD)_2PHAL$, 3 eq. K_3FeCN_6/
3 eq. K_2CO_3/1 eq. $MeSO_2NH_2$ in 1:1 *t*-BuOH/H_2O, 0 °C

Treatment of **15** with a catalytic amount of palladium and triphenylphosphine (1% $Pd_2(dba)_3$•$CHCl_3$/2.5% PPh_3) and a mild hydride source (Et_3N/HCO_2H) afforded an excellent yield (85%) of the desired δ-hydroxy ester **16** as a 3:1 (trans/trans to trans/cis) mixture of γ,δ-double bond isomers. This 3:1 mixture of double bond isomers was easily converted into a 9:1 mixture by exposure to a catalytic amount of I_2 in the presence of light (3500 Å). However, the photochemical isomerization was not needed when triphenylphosphine was not used in the palladium-catalyzed reduction. Running the reaction in the absence of triphenylphosphine (1% $Pd_2(dba)_3$•$CHCl_3$, 3 equiv of Et_3N/HCO_2H), *trans*,*trans*-7-hydroxydienoate **16** was produced as a 7:1 mixture of double-bond isomers in excellent yield (93%).[21]

Scheme 4

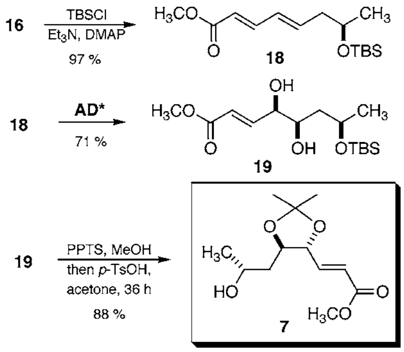


AD* = 1% OsO_4,1.1% $(DHQD)_2PHAL$/ 3 eq. K_3FeCN_6
3 eq. K_2CO_3/1 eq. $MeSO_2NH_2$/3 eq. $NaHCO_3$ in 1:1 *t*-BuOH/H_2O, 0°C

With the C-7 hydroxyl and diene functionality stereoselectively installed, we next addressed the selective introduction of the remaining C-4 and C-5 hydroxyl groups by means of another asymmetric dihydroxylation reaction (Scheme 4). Treatment of diene **16** with typical asymmetric dihydroxylation conditions, including the addition of 3 equiv of $NaHCO_3$, afforded triol **17**.[22] Isolation of triol **17** proved to be difficult; therefore, the crude reaction mixture was filtered through a pad of Celite, followed by a pad of Florisil, and directly subjected to acetonide protection conditions to yield acetonide **7** in modest overall yield over two steps (54%).

A higher yielding and more reproducible procedure (Scheme 5) for the preparation of **7** evolved after first protection of alcohol **16** as a TBS ether to yield dienoate **18** (98%). The asymmetric dihydroxylation of **18** using the same buffered conditions[22] produced TBS-protected triol **19** in good yield (71%).[23] One-pot protection as the acetonide and removal of the TBS group produced acetonide **7** (88%).

Scheme 5



AD* = 1% OsO_4,1.1% $(DHQD)_2PHAL$/ 3 eq. K_3FeCN_6
3 eq. K_2CO_3/1 eq. $MeSO_2NH_2$/3 eq. $NaHCO_3$ in 1:1 *t*-BuOH/H_2O, 0°C

Having synthesized the two halves of colletodiol, we turned our attention to the fragment coupling (alcohol **7** plus carboxylate **8**) and the ensuing conversion of **20** to colletodiol **1** (Scheme 6). Alcohol **7** was esterified with acid **8** using 2,4,6-trichlorobenzoyl chloride in 77% yield. Removal of the TBS group was accomplished using TBAF to yield compound **20** in 79% yield. The addition of 1 equiv of LiOH selectively hydrolyzed the methyl ester of **20** yielding hydroxy acid **6** in good yield (79%).[24,25]

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(19) Sharpless has shown that the AD-mix reagent dihydroxylates simple dienoates and trienoates with good enantio- and diastereocontrol; see: (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571. (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−76.

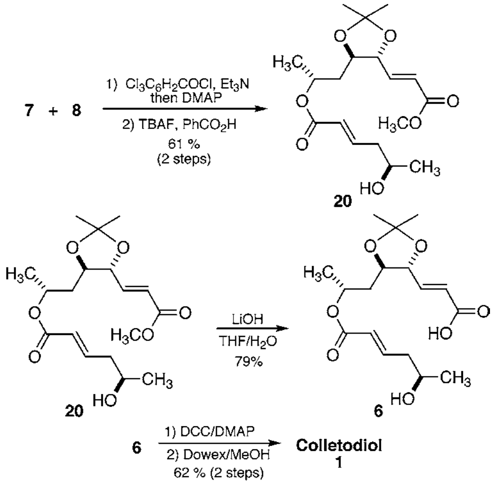
(20) An interesting aspect of this reaction is that the stereochemical configuration, as well as, the electron withdrawing nature of the 6-hydroxy group of **14** protect the dienoate against further oxidation to a tetraol. This is evident from the observation that once the 6-hydroxyl group of **14** was removed (as in **16**) the substrate readily oxidizes (**16** to **17**) under the AD-mix conditions.

(21) This mixture could be used in the next step without separation of the double-bond isomers because the trans/cis diene isomer of **16** dihydroxylates at a much slower rate, see ref 23.

(22) Sharpless has suggested that buffering the AD-mix reaction with $NaHCO_3$ can help prevent base-catalyzed side reactions; see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

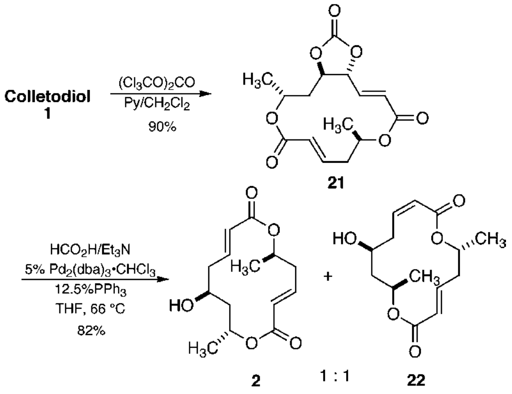
(23) Diol **19** was isolated in a 71% yield along with ~10% of the regioisomeric diol product and ~5% of the recovered trans/cis diene isomer of **16**.

Scheme 6



The spectral data for hydroxy-acid **6** matched the data obtained by Keck.[5b] Following Keck's procedure for macrolactonization (DCC/DMAP, 72%) and deprotection (Dowex/MeOH, 86%), **6** was cleanly converted into colletodiol in good overall yield (62%). The synthetic material had spectral data that matched that recorded for the isolated material (^{1}H NMR, ^{13}C NMR, IR, and optical rotation). This enantioselective route to colletodiol required only 11 steps and produced sufficient quantities (12% overall yield) for further synthetic studies (vide infra).

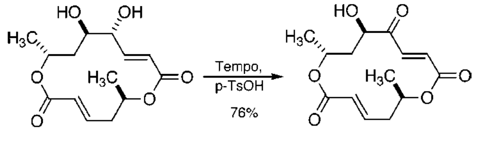
Scheme 7



Because one of the two hydroxyl groups in colletodiol is allylic, it was envisioned that colletol **2** could be synthesized using the same palladium-catalyzed reduction (Scheme 7). Efforts to achieve this transformation started with the formation of the cyclic carbonate **21** of colletodiol. Treatment of colletodiol with triphosgene yielded the cyclic carbonate in excellent yield (90%). The palladium-catalyzed reduction on this cyclic carbonate produced colletol **2**, and, unfortunately, its double bond isomer **22** in a 1:1 mixture (82% combined yield). On the basis of the results for the conversion of **15** to **16**, the reaction was attempted in the absence of triphenylphosphine; however, no product was obtained as the palladium precipitated out of solution. To determine whether the double bond isomer **22** was formed from the π-allyl reaction or from a subsequent double bond isomerization of **1** under the reaction conditions, both **2** and **22** were reexposed to the reaction conditions and no double bond isomerization occurred. In fact, all attempts to isomerize the *cis*-double bond to the *trans*-double bond (I_2, $h\nu$; PhSH, AIBN) were unsuccessful.

It was similarly envisioned that grahamimycin A **4** could be synthesized by a selective oxidation of the allylic alcohol of colletodiol **1** (Scheme 8). Attempts at this selective oxidation using MnO_2, DDQ, and Dess−Martin periodinane were unsuccessful. While grahamimycin A could be observed from the Dess−Martin conditions, a clean conversion resulted upon the use of a TEMPO oxidation. Thus, treatment of colletodiol with 2 equiv of TEMPO and *p*-TsOH produced grahamimycin A in good yield (76%).

Scheme 8



Colletodiol
1

Grahamimycin A
4

In conclusion, a short and enantioselective synthesis of colletodiol has been developed in which all the stereocenters were established by the Sharpless asymmetric dihydroxylation. The overall route is comparable in length and efficiency with previous routes, providing colletodiol in 11 longest linear steps (16 total steps). The synthesis provides colletodiol in 12% overall yield (87% average yield) and is amenable for the preparation of either enantiomer. Colletol and its *cis*-double-bond isomer **22** were synthesized from colletodiol using the same palladium-catalyzed reduction. Grahamimycin A was synthesized from colletodiol using a TEMPO oxidation. Further studies on the use of this catalytic Os/Pd-oxidation/reduction sequence for the preparation of other macrolactone antibiotics as well as colletodiol analogues will be reported in due course.

Acknowledgment. We thank the Arnold and Mabel Beckman Foundation for their generous support of our program.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For our route, this selective hydrolysis of the methyl ester was a significant improvement. Most previous syntheses of colletodiol used either a thioester, allyl ester, or β-sulfonylethyl ester to differentiate the two carboxylates, which we believed would not be compatible with our approach.

(25) The methyl ester could also be deprotected with excess LiI in refluxing pyridine.