Efficient Synthesis of (+)-Kalafungin and (–)-Nanaomycin D by Asymmetric Dihydroxylation, Oxa-Pictet–Spengler Cyclization, and H_2SO_4-Mediated Isomerization

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Abstract: The pyranonaphthoquinone antibiotics and antitumor agents (+)-kalafungin (**1**) and (–)-nanaomycin D (**3** = *ent*-**1**) were synthesized from 1,5-napthalenediol (**13**) in 11 steps. Stereocontrol was high: 99.5 ee/93% diastereoselectivity for **1**, 98.5% ee/94% diastereoselectivity for **3**. Enantiocontrol was achieved by the asymmetric dihydroxylation of the β,γ-unsaturated ester **9**. Diastereocontrol was realized in the final step by an almost complete epimerization in H_2SO_4.

Key words: β,γ-unsaturated carboxylic esters, butyrolactones, epimerization, quinones, pyranonaphthoquinones

The quinone moiety is present in a significant number of natural products.[1] These comprise such biologically important compounds as the anthracyclinone and mitomycin anticancer agents, antibiotics, fungicides, and anticoccidial agents. The naturally occurring naphthoquinones kalafungin[2] (**1**), frenolicin B[3] (**2**), nanaomycin D[4] (**3**), nanaomycin A[5] (**4**), medermycin[6] (**5**), and granaticin[7] (**6**) are members of the growing family of the pyranonaphthoquinones (Figure 1),[8] which possess antimicrobial and antitumor activities.[9]

An intriguing feature of the core structure of the pyranonaphthoquinones is that the relative configurations of the stereocenters at C-3a, C-5, and C-11b are fixed while the absolute configuration may be either one. As a consequence, kalafungin (**1**) and nanaomycin D (**3**) are pyranonaphthoquinones, which are enantiomers. Moreover, the absolute configurations encountered in the former compound (**1**) recur in many other pyranonaphthoquinones – e. g., in medermycin (**5**) – as do the absolute configurations of the latter (**3**) – e. g., in granaticin (**6**). This structural feature, the desire to develop strategies for the construction of unnatural analogs, and the challenge to design methodology also applicable to the synthesis of the structurally more demanding representatives of this class of compounds (e. g., structures **5** and **6**) prompted many investigations.[8] With respect to kalafungin (**1**) and nanaomycin D (**3**), most synthetic efforts have led to racemic material, i.e., 50:50 mixtures of **1** and **3**.[10] Only two enantioselective syntheses of compound **3** and one of **1** have been reported to date.[11] No matter whether racemic or enantiopure material was the target, the greatest challenge in all previous approaches was establishing the *trans*-relationship between the substituents at positions C-3a and C-5 of the dihydropyran ring.

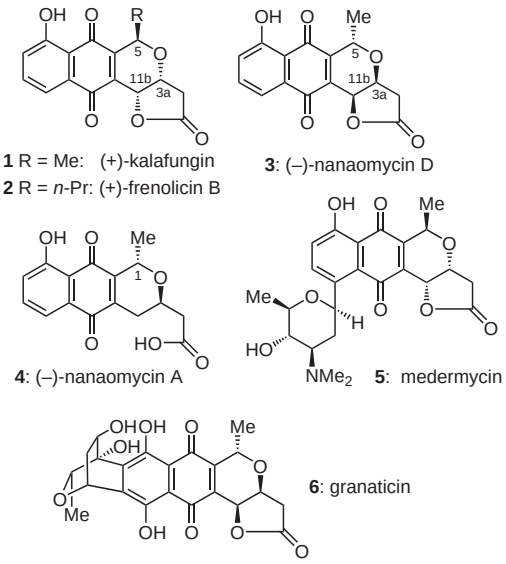

Figure 1 Naturally occurring pyranonaphthoquinones.

Our research group has been actively involved in the stereoselective synthesis of saturated and unsaturated butyrolactones by asymmetric dihydroxylation[12] ('AD') of β,γ-unsaturated esters. This provides β-hydroxy-γ-butyrolactones in a single step and essentially enantiomerically pure.[13] Since kalafungin (**1**) and nanaomycin D (**3**) are O-benzylated β-hydroxy-γ-butyrolactones, we engaged in their syntheses, hoping to further the scope of our strategy.

Adopting this concept entailed establishing the stereochemistry at C-3a and C-11b of targets **1** and **3** by the asymmetric dihydroxylation of the β,γ-unsaturated ester **9**, employing AD-mix β® (→ **10**) and α® (→ *ent*-**10**), respectively (Scheme 1). The majority of the unsaturated esters, which we dihydroxylated in our previous lactone syntheses were prepared from an aldehyde (cf. **7**) and methyl malonate (**8a**) or malonic acid (**8b**) by[13e,f] – or following[13d,f] – a decarboxylative deconjugative Knoevenagel condensation.[14] In a single instance, we accessed a β,γ-unsaturated ester substrate for asymmetric butyrolactone formation differently,[13g] namely through the Arndt–

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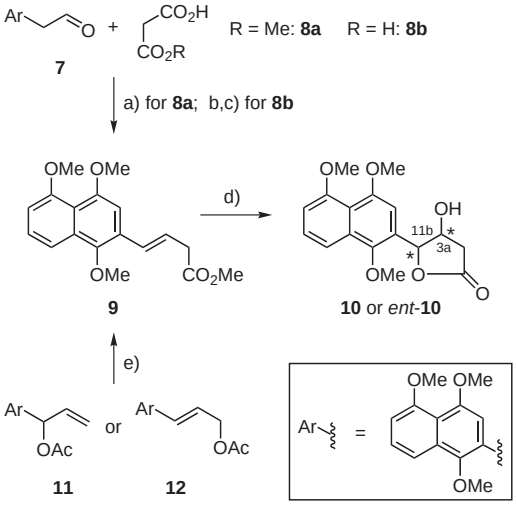
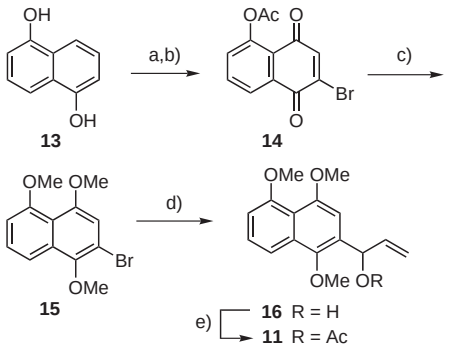
Eistert homologation of an α,β-unsaturated carboxylic acid.[15] However, this *modus procedendi* lacks scope and, according to our study of substituent effects,[16] probably would not suit to obtain **9**. We neither pursued a Knoevenagel route to β,γ-unsaturated ester **9** since the substrate aldehyde **7** did not look readily accessible – nor did we reproduce the published synthesis[17] because it involved 5 steps from a very expensive starting material (3-bromojuglone). Rather, we opted for making use of Tsuji's Pd-catalyzed carbonylation of allyl acetates in methanol[18] for making ester **9** available. Of the two conceivable acetates **11** or **12** we selected **11** as a precursor and synthesized it as shown in Scheme 2.



Scheme 1 *Strategic considerations*: a), b) decarboxylative deconjugative Knoevenagel condensation; c) esterification; d) asymmetric dihydroxylation; e) CO, cat. PdL_x, MeOH.



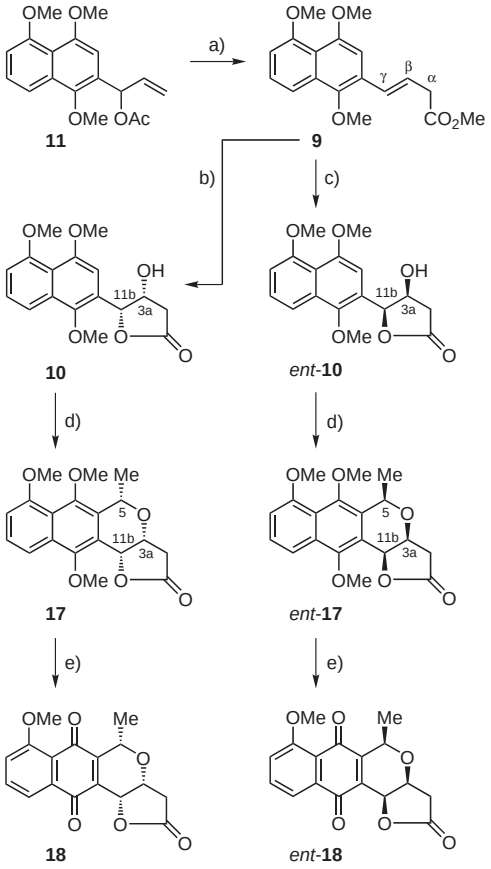
Scheme 2 *Reagents and conditions*: a) Ac_2O (3.8 equiv), Et_3N (3.0 equiv), DMAP (3 mol%), CH_2Cl_2, r.t., 24 h, 87% (ref.[19b]: 89%); b) NBS (4.1 equiv), aq HOAc, 55 °C, 2 h, 92% (ref.[19b]: 84%); c) $Na_2S_2O_4$ (3.0 equiv), *n*-Bu_4NBr (5 mol%), THF–H_2O (4:3), r.t., 5 min, KOH (9.8 equiv), r.t., 15 min, Me_2SO_4 (15 equiv), r.t., 12 h, 80%; d) *n*-BuLi (1.01 equiv), THF, –85 °C, 10–15 s, acrolein (2.5 equiv), 20 min, then r.t., 1 h, 70%; e) Ac_2O (2.0 equiv), Et_3N (2.0 equiv), DMAP (9 mol%), CH_2Cl_2, r.t., 8 h, 85%.

Inexpensive 1,5-naphthalenediol (**13**) was bisacetylated and then brominated/oxidized giving naphthoquinone **14** in slightly better yield (80%) than reported (75%;[19] Scheme 2). Ref.[19] continued towards the bromotrimethoxynaphthalene **15** in 4 steps. We shortcut this to a single operation: acetoxyquinone **14** was reduced with $Na_2S_2O_4$ in aq THF; solid KOH was added in order to obtain the trisnaphtholate; treatment with dimethyl sulfate gave bromotrimethoxynaphthalene **15** – in twice (80%) the published yield. Br/Li exchange with *n*-BuLi at –85 °C in THF and quenching with acrolein no more than 10–15 s later provided 70% of allyl alcohol **16**;[20] higher temperatures or prolonged reaction times with *n*-BuLi decreased the yield at the expense of an increased fraction of the protonation product (1,4,5-trimethoxynaphthalene). Acetylation of compound **16** completed the synthesis of allyl acetate **11** (85% yield).

The ensuing Tsuji carbonylation was intended to convert allyl acetate **11** into deconjugated ester **9** (Scheme 3). Rather than trying Tsuji's catalysis by $PdCl_2$[18a] we relied on the modified conditions of Murahashi et al. – catalysis with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of Ph_3P, and NaBr.[18b] They usually provide higher yields and also performed well for our substrate **9**. However, we isolated around 80% of a mixture of unsaturated esters, namely the β,γ-unsaturated ester **9** (major product) and the α,β-unsaturated isomer (minor product). These components were inseparable by flash chromatography on silica gel.[21] The shorter the reaction time, the lesser α,β-unsaturated isomer resulted: the β,γ:α,β ratio was 85:15 after 18 hours, 90:10 after 8 hours, and 95:5 after 5–6 hours. In the latter case the combined yield was 83%.[22]

The asymmetric dihydroxylation of **9** was performed following the standard procedure[12] (Scheme 3): with $(DHQD)_2$-PHAL as the stereoinducing ligand we obtained hydroxylactone **10** (82%) and with $(DHQ)_2$-PHAL the hydroxylactone *ent*-**10** (79%). Enantioselectivities were excellent (99.5% and 98.5% ee, respectively), as revealed by chiral HPLC.[23] Following literature precedence,[24] the tetracyclic dihydropyrans **17** (92%) and *ent*-**17** (91%) resulted from treatment of hydroxylactones **10** and *ent*-**10**, respectively, with the dimethylacetal of acetaldehyde in the presence of $BF_3{\cdot}OEt_2$; this transformation entails generation of a mixed acetal, equilibration with a carboxonium ion, and ring-closure of the latter through an ArS_E – or oxa-Pictet–Spengler – reaction. The dihydropyran moieties of products **17**/*ent*-**17** resulted diastereomerically pure, their substituents being oriented ^{5,3a}*cis*,^{3a,11b}*cis*,[25] i.e., as in many related cases.[10b,24,26] Cerium ammonium nitrate (CAN) oxidations of compounds **17** and *ent*-**17** ensued, giving rise to quinones **18** (87%) and *ent*-**18** (88%), respectively, fully conserving their configurational integrities.[27]

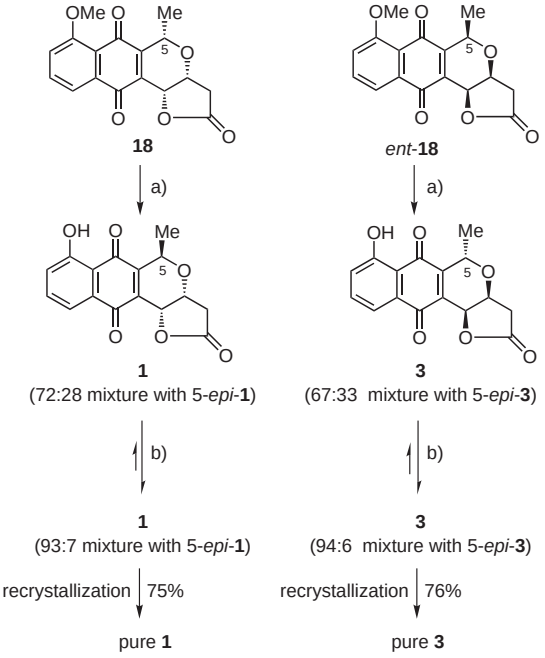
What remained to be done was (1) cleaving the aromatic ether and (2) altering the configuration at C-5 (Scheme 4). Gratifyingly, demethylation of compound **18** with 9 equivalents of BBr_3 was accompanied by substantial inversion of configuration at C-5,[28] delivering 82% of a 72:28 mixture of the desired pyranonaphthoquinone kalafungin (**1**) and the undesired epimer 5-*epi*-**1**. Similarly, demethylation of *ent*-**18** with 3 equivalents of BBr_3 furnished 84% of a 67:33 mixture of nanaomycin D **3** and



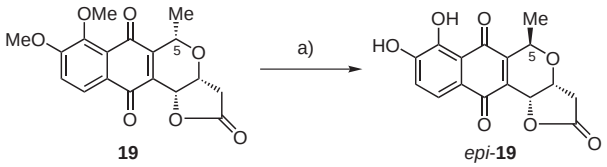
Scheme 3 *Reagents and conditions*: a) $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol%), Ph_3P (8.0 mol%), NaBr (25 mol%), *i*-Pr_2NEt (1.0 equiv), MeOH, CO (30 atm), 50 °C, 6 h, 83% (95:5 mixture with the α,β-unsaturated isomer); b) 95:5 mixture of **9** and its α,β-unsaturated isomer, $(DHQD)_2$-PHAL (1.0 mol%), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $NaHCO_3$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), $K_2Os_2(OH)_4$ (0.4 mol%), *t*-BuOH–H_2O (1:1), 0 °C, 24 h, then r.t., 12 h, 82% (relative to the fraction of **9** in the substrate); c) same as b) except that a 90:10 mixture of **9** and its α,β-unsaturated isomer and $(DHQ)_2$-PHAL (1.0 mol%) were used, 79% (relative to the fraction of **9** in the substrate); d) $H_3CCH(OMe)_2$ (2.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), Et_2O–THF (4:1), r.t., 12 h, 92% (**17**), 91% (*ent*-**17**); e) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv), MeCN–H_2O (1:1), r.t., 15 min, 87% (**18**), 88% (*ent*-**18**).

its C-5 epimer. These epimerizations had been hoped for but had not progressed as far as expected based on the closely related demethylation/epimerization **19** → *epi*-**19**[29] (Scheme 5). However, when we stirred either of the epimeric mixtures in concentrated sulfuric acid[30] for 30 minutes, the γ-lactone rings stayed untouched while the epimerizations[28] proceeded further: the desired products were now contained in 93:7 **1**:5-*epi*-**1** and 94:6 **3**:5-*epi*-**3** mixtures. A single recrystallization of these specimens from pentane–CH_2Cl_2 afforded pure (+)-kalafungin (**1**)[31] and, similarly, pure (–)-nanaomycin D (**3**).[32] The spectroscopic data of these compounds agreed fully with the ones reported.[11b]

In summary, we executed 11-step asymmetric syntheses both of (+)-kalafungin (**1**) and (–)-nanaomycin D (**3**). Sharpless' asymmetric dihydroxylation was the single source of enantioselectivity. Oxa-Pictet–Spengler cyclizations afforded the pyranolactone-annulated naphthalenes **17** and *ent*-**17** with the ^{5,3a}*cis*,^{3a,11b}*cis* geometry. Concentrated H_2SO_4 isomerized the corresponding pyranolactone-annulated naphthoquinone mixtures **1**/5-*epi*-**1** and **3**/5-*epi*-**3** such that the ^{5,3a}*trans*,^{3a,11b}*cis* stereorelationships of **1** and **3** arose with 93:7 and 94:6 preponderances, respectively.



Scheme 4 *Reagents and conditions*: a) BBr_3 (9 equiv for **18**, 3.0 equiv for *ent*-**18**), CH_2Cl_2, –50 °C, 25 min, then r.t., 2 h, 82%, 84%; b) in concd H_2SO_4, r.t., 30 min, 87%, 90% .



Scheme 5 *Reagents and conditions*: a) ref.[29]: BBr_3 (3.3 equiv), CH_2Cl_2, –48 °C, 5 min, r.t., 1 h, 87%.

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(22) Methyl (*E*)-4-(1,4,5-trimethoxynaphth-2-yl)-3-butenoate (**9**): NaBr (97.6 mg, 0.948 mmol, 25 mol%), Ph_3P (79.6 mg, 0.303 mmol, 8 mol%), $Pd_2(dba)_3CHCl_3$ (78.5 mg, 0.076 mmol, 2 mol%), and *i*-Pr_2NEt (0.63 mL, 0.49 g, 3.80 mmol) were added sequentially to a solution of allyl acetate **11** (1.200 g, 3.793 mmol) in MeOH (5 mL). The reaction mixture was pressurized with CO (30 atm) in an autoclave and stirred at 50 °C for 6 h before cooling to r.t., quenching with H_2O, and extraction with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed twice with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using cyclohexane–EtOAc (17:3 → 3:1) as an eluent to give **9** (1.001 g, 83%; 95:5 mixture with the isomeric α,β-unsaturated ester) as a yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ = 3.35 (dd, $J_{2,3}$ = 7.1 Hz, $^4J_{2,4}$ = 1.5 Hz, 2-H), 3.71 (s, MeO_2C), 3.83, 3.93, and 3.96 (3 s, 3 × MeO), 6.40 (dt, $J_{3,4}$ = 16.2 Hz, $J_{3,2}$ = 7.1 Hz, 3-H), 6.82 (br d, $J_{6',7'}$ = 7.8 Hz, 6′-H), 6.93 (s, 3′-H), 6.96 (dt, $J_{4,3}$ = 16.2 Hz, $^4J_{4,2}$ = 1.5 Hz, 4-H), 7.38 (dd, $J_{7',6'} = J_{7',8'}$ = 8.1 Hz, 7′-H), 7.68 (dd, $J_{8',7'}$ = 8.4 Hz, $^4J_{8',6'}$ = 1.1 Hz, 8′-H).
(23) The enantioselectivities were determined by HPLC. Column: Chiralcel OD-H No. ODHOCE-AJ071; Daicel Chemical Ind. Ltd.; eluent: *n*-heptane–EtOH (60:40); flow rate; 0.6 mL/min; UV detector: 233 nm; t_R: 12.3 min for **10**, 14.7 min for *ent*-**10**.
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(25) This was inferred from the high-field shifts of the italicized resonances in our ^{1}H NMR spectrum (500 MHz, $CDCl_3$; $\delta_{3a\text{-}H}$ = *4.37*, $\delta_{5\text{-}H}$ = *5.07*, and $\delta_{11b\text{-}H}$ = 5.59 ppm) relative to the values published (ref.[11b]) for the *trans*,*cis*-isomer: $\delta_{3a\text{-}H}$ = *4.73*, $\delta_{5\text{-}H}$ = *5.37*, and $\delta_{11b\text{-}H}$ = 5.58 ppm. Ref.[10f] reports a similar shift difference for the analogous signals of *cis*,*cis*-**20** (δ values in analogous order: δ = *4.27*, *4.84*, and 5.33 ppm) vs. *trans*,*cis*-**20** (δ values in analogous order: δ = *4.61*, *4.96*, and 5.33 ppm). See Figure 2.

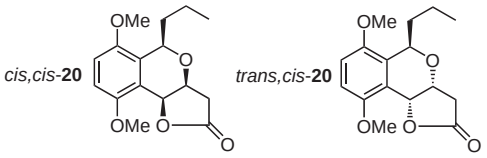

Figure 2

(26) Seizable fractions of the [5,3a]*trans*,[3a,11b]*cis*-isomer accompany [5,3a]*cis*,[3a,11b]*cis*-dihydropyran formation only when exposure to acid is longer than required for ring-formation alone: (a) Ref.[24d] reports a dihydropyran annulation using HCl (gaseous) and benzaldehyde; *cis*,*cis*:*trans*,*cis* ratios were 94:6 after 5 min at –5 °C and 16:84 after 2 h at r.t. (b) Ref.[24g] describes a related dihydropyran generation using HCl and butanal at 25 °C; *cis*,*cis*:*trans*,*cis* ratios were 84:16 after 3 h and 22:78 after 8 h.

(27) CAN oxidation of the C-5 epimer of *ent*-**17**. See ref.[11b]

(28) The mechanism of the Lewis acid (BBr_3)- or Brønsted acid (H_2SO_4)-mediated epimerization at C-5 of dihydropyranonaphthoquinones **18**, 5-*epi*-**1**, and their enantiomers has not been investigated. We assume that neither C^5–Ar nor C^5–O bond cleavage but enone ⇆ dienol (as exemplified by formulas **21** and/or **22**) tautomerism causes the configurational change. See Figure 3.

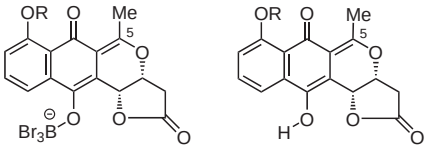

Figure 3

(29) Brimble, A. M.; Phythian, S. J.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2855.

(30) H_2SO_4-mediated epimerizations of lactone-free dihydropyranonaphthoquinones: (a) 0:100 *trans*-**23**:*cis*-**23** → 67:33 (ref.[10b]); (b) 50:50 *trans*-**23**:*cis*-**23** → 67:33. See: Uno, H. *J. Org. Chem.* **1986**, *51*, 350. (c) 60:40 *trans*-**24**:*cis*-**24** → 80:20 (ref.[24e]). (d) Related isomerization of the more highly substituted dihydropyranonaphthoquinone **25** (Figure 4): see ref.[11b]

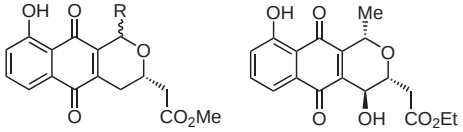

Figure 4

(31) $[\alpha]_D^{20}$ +160.6 (*c* 0.3, $CHCl_3$); mp 168–170 °C. Ref.[11b] $[\alpha]_D^{24}$ +160 (*c* 0.3, $CHCl_3$); mp 171–173 °C.

(32) $[\alpha]_D^{20}$ –159.7 (*c* 0.35, $CHCl_3$); mp 169–171°C. Ref.[11b] $[\alpha]_D^{24}$ –163 (*c* 0.44, $CHCl_3$); mp 171–173 °C.