A Novel Synthesis of the 2-Aminoimidazol-4-carbaldehyde Derivatives, Versatile Synthetic Intermediates for 2-Aminoimidazole Alkaloids

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Abstract: The title synthesis was achieved by the reaction of *t*-butoxycarbonylguanidine with 3-bromo-1,1-dimethoxypropan-2-one as a key step. Starting with 1-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminoimidazol-4-carbaldehyde thus obtained expeditious synthesis of oroidin, hymenidin, dispacamide and monobromodispacamide, the representative 2-aminoimidazole alkaloids, was accomplished.

Key words: 2-aminoimidazol-4-carbaldehydes, alkaloids, cyclizations, total synthesis, heterocycles

Various structural types of 2-aminoimidazole alkaloids including oroidin (**1**), hymenidin (**2**), dispacamide (**3**), monobromodispacamide (**4**), sceptrin (**5**) and ageladine A (**6**), have been isolated from marine sources (Figure 1).[1] Their intriguing structures as well as diverse biological activities, some of which are of interest from the pharmaceutical points of view, make these alkaloids attractive synthetic targets, and numerous total syntheses have hitherto been reported.[1,2]

Taking into account the synthetic steps for constructing their characteristic 2-aminoimidazole moieties, the total syntheses so far achieved can be roughly classified into two categories. One is the synthetic step where the 2-aminoimidazole ring is produced by condensing a guanidine derivative with an α-haloketone[3] or by reacting cyanamide with an α-aminoketone.[2a] The other step features amination of the 2-position of the preformed imidazole ring by the use of explosive azide or diazonium reagents.[4] In both syntheses, the construction of the 2-aminoimidazole moiety is usually carried out at the later synthetic stages. Accordingly, it is obvious that a number of the congeners for natural 2-aminoimidazole alkaloids in which the structures except for the 2-aminoimidazole moiety are replaced with various structural motifs different from those involved in natural products, cannot be readily prepared in a large scale by applying the reported methods.

Considering these facts delineated above, a novel synthetic strategy was sought which can afford not only natural 2-aminoimidazole alkaloids but also their congeners more efficiently than the methods reported.[1] We have now found that the 2-aminoimidazol-4-carbaldehyde derivatives **I** (Figure 2) would be the best starting material for the novel strategy. In addition to the characteristic 2-aminoimidazole moieties, **I** carry the 4-aldehyde groups that

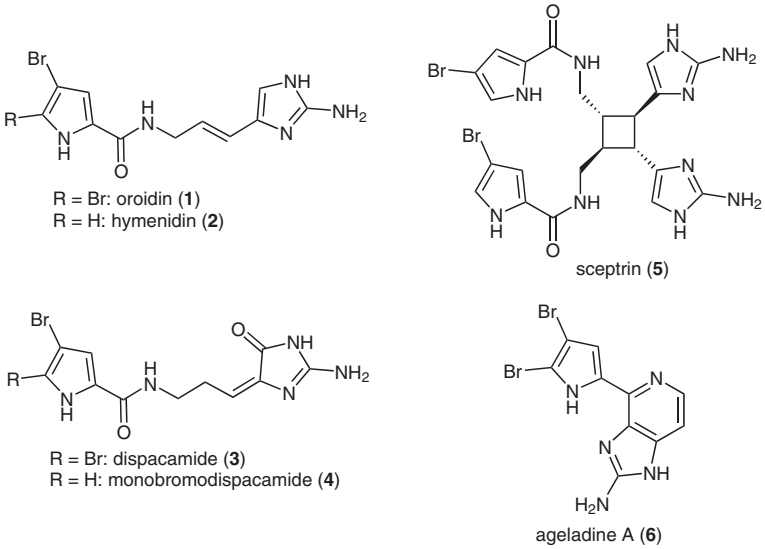

Figure 1 Structures of representative 2-aminoimidazole alkaloids

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can be elaborated to various structural motifs. However, a search of the literature soon disclosed that the synthesis of **I** is scarcely explored. The only method reported by Alain[5] is anticipated to lack practicality due to its harsh reaction conditions such as thermolysis. Therefore, we embarked on exploring a novel synthetic route to **I** more efficient than that reported.[5]

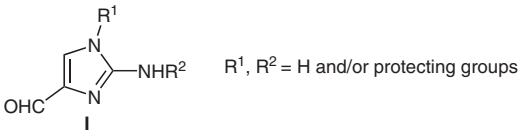
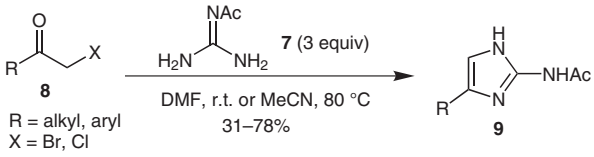


Figure 2 Structures of 2-aminoimidazol-4-carbaldehyde derivatives.

It was reported by Webber et al.[6] that, as shown in Scheme 1, the 2-acetamido-4-alkyl- or 4-arylimidazole derivatives **9** can be prepared in good yields by the reaction of acetylguanidine (**7**) and α-haloketones **8** in *N*,*N*-dimethylformamide or acetonitrile. Expecting that applying the Webber reaction can readily produce **I**, we treated 3-bromo-1,1-dimethoxypropan-2-one (**10**) with **7** under the same conditions as employed by Webber et al.[6] However, as shown in Scheme 2, the desired product **11**[7] was obtained only in 1% yield along with complex reaction products.[8] Aiming to improve the disappointing results, the same reaction was next examined by using *tert*-butoxycarbonylguanidine (**12a**)[9] in place of **7**. While it was reported that **12a** is usable for the Webber reaction similarly to **7**,[3a] the reaction of **10** with **12a** had not been examined. To our delight, the reaction was found to take place smoothly, affording 2-amino-1-*tert*-butoxycarbonyl-4-dimethoxymethylimidazole (**14a**)[7] as the sole product in 47% yield.[8] Formation of the expected 2-*tert*-butoxycarbonylamino-4-dimethoxymethylimidazole (**13a**) corresponding to **9** and **11** was not observed at all. This result distinctly differs from that reported.[3a]



Scheme 1 Synthesis of the 4-substituted-2-acetamidoimidazole derivatives reported by Webber et al.[6]

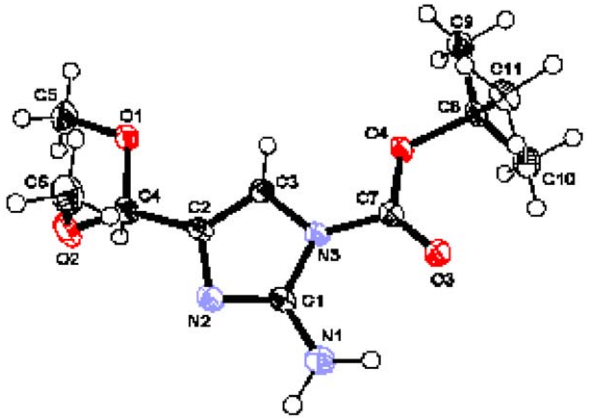
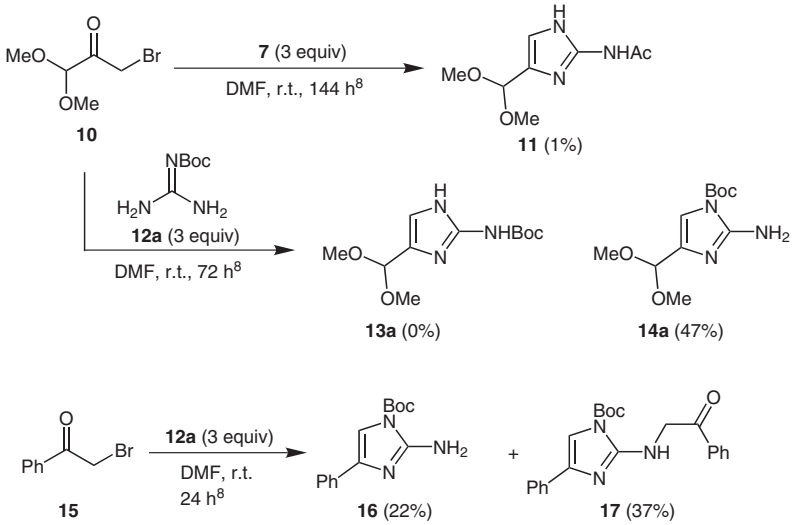


Figure 3 X-ray crystal structure of compound **14a**

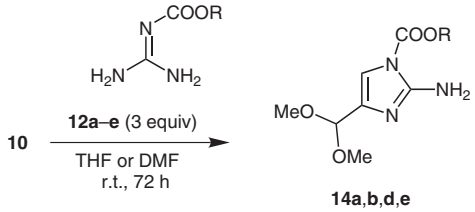
The structure of **14a** was verified by its spectral data[7] and single-crystal X-ray analysis (Figure 3).[10] Interestingly, when phenacyl bromide (**15**) being one of the typical substrates for the Webber reaction[6] was used in place of **10**, a mixture of 2-amino-1-*tert*-butoxycarbonyl-4-phenylimidazole (**16**) and its 2-phenacyl derivative **17** was similarly obtained in 22% and 37% yields, respectively.[11] In this reaction too, formation of the 2-*tert*-butoxycarbonylamino derivative corresponding to **9** and **11** could not be detected. The reason why **12a** gave the results obviously different from those obtained with **7** is presently quite unclear. However, an electronic effect rather than a steric effect may account for the observed results.



Scheme 2 Reactions of the acylguanidine derivatives (**7** and **12a**) with 3-bromo-1,1-dimethoxymethylpropan-2-one (**10**)

The novel reaction to cleanly afford **14a** from **10** and **12a** was further studied by employing various alkoxycarbonylguanidines **12b–e** and changing the reaction conditions. These results are summarized in Table 1 and 2. It appeared evident that **12a** is the best alkoxycarbonylguanidine of choice and the chemical yield is almost unaffected by the nature of the reaction solvent. The best yield realized by using **12a** is probably due to its stability under the basic reaction conditions intensified by the increased steric hindrance. Under the optimized conditions (Table 1, run 2),[12] **14a** could be produced in more than 60% yield.

Table 1 Synthesis of Various 2-Amino-1-alkoxycarbonyl-4-dimethoxymethylimidazole Derivatives (**14a**,**b**,**d**,**e**) in THF or DMF[a]



Entry	Product R	Yield (%)[b] in THF	in DMF
1	*t*-Bu (**14a**)	51	47
2[c]	*t*-Bu (**14a**)	62 (64[d])	
3	Me (**14b**)	<24[e]	<8[e]
4	CH_2CCl_3 (**14c**)	n.d.[f]	n.d.[f]
5	Allyl (**14d**)	24	26
6	Benzyl (**14e**)	37	26

[a] All reactions were carried out on 0.25–1.0-mmol scale.
[b] Isolated yield.
[c] The reaction was performed at 50 °C for 6 h.
[d] The reaction was carried out on 10-mmol scale.
[e] This sample was contaminated by a minute amount of the unidentified byproduct.
[f] Not detected.

Table 2 Synthesis of 2-Amino-1-*tert*-butoxycarbonyl-4-dimethoxymethylimidazole (**14a**) in Various Solvents[a]

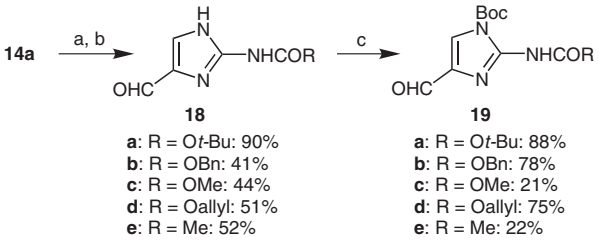
10 —(**12a** (3 equiv), r.t., 72 h)→ **14a**

Entry	Solvent	Yield (%)[b]	Entry	Solvent	Yield (%)[b]
1	PhMe	42	6	MeCN	38
2	EtOAc	50	7	DMA[c]	47
3	THF	51	8	DMF	47
4	CH_2Cl_2	40	9	NMP[d]	44
5	EtOH	44	10	DMSO	51

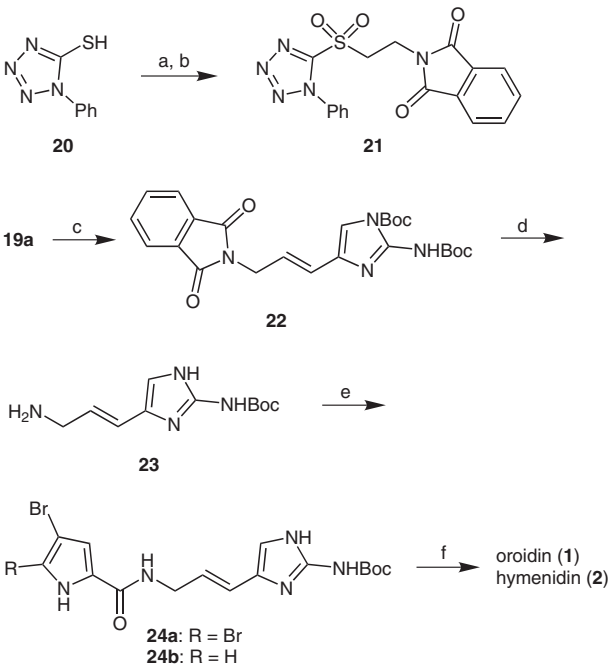
[a] All reactions were performed on 0.25-mmol scale.
[b] Isolated yield.
[c] *N*,*N*-Dimethylacetamide.
[d] *N*-Methylpyrrolidone.

As shown in Scheme 3, **14a** which becomes readily available in a large quantity was converted to 2-acylaminoimidazo-4-carbaldehydes **18** corresponding to **I** by sequential acylation and deacetalization. Further protection of the 1-imino group in **18** with a *tert*-butoxycarbonyl group furnished 2-acylamino-1-*tert*-butoxycarbonylimidazol-4-carbaldehyde **19** which also corresponds to **I**. Attempted introduction of protective groups other than the *tert*-butoxycarbonyl group into the 1-imino group of **18a** turned out fruitless.[13]

With paving the way to **19** completed, the total synthesis of representative 2-aminoimidazole alkaloids, oroidin (**1**), hymenidin (**2**), dispacamide (**3**) and monobromodispacamide (**4**), was next examined to explore the synthetic utility of **19**. Thus, as outlined in Scheme 4, Julia



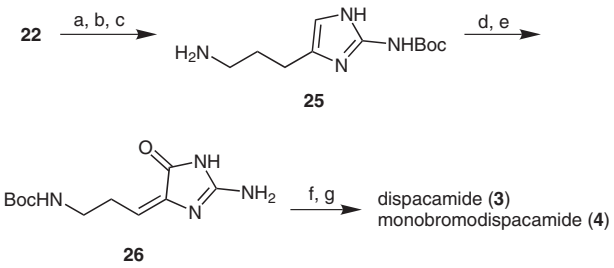
Scheme 3 Synthesis of various 2-aminoimidazole-4-carbaldehyde derivatives (**18a–e** and **19a–e**) from 2-amino-1-*tert*-butoxycarbonyl-4-dimethoxymethylimidazole (**14a**). *Reagents and conditions*: (a) $(RCO)_2O$ or RCOCl, NaHMDS (2 equiv)–THF, 0 °C–r.t., 15 min; (b) PPTS (cat.)–acetone–H_2O (3:2), r.t., overnight; (c) Boc_2O, TEA–THF–MeCN (1:1), r.t., 8 h.



Scheme 4 Total synthesis of oroidin (**1**) and hymenidin (**2**). *Reagents and conditions*: (a) *N*-(2-bromoethyl)phthalimide, K_2CO_3, acetone, reflux, 3 h; (b) MCPBA, $NaHCO_3$–CH_2Cl_2, r.t., overnight, 79% (2 steps from **20**); (c) **21**, NaHMDS–THF, –78 °C, 30 min, 62%; (d) H_2NNH_2–EtOH, 50 °C, 2 h, 92%; (e) 4,5-dibromo- or 4-bromo-2-trichloroacetylpyrrole, Na_2CO_3–DMF, r.t., overnight, 79% for **24a**, 83% for **24b**; (f) 20% HCl–EtOH, r.t., 1 h, 92% for **1**, 99% for **2**.

olefination[14] of **19a** with sulfone **21** gave *E* olefin **22** in 62% yield along with the undesired *Z* olefin (10% yield). Wittig reaction to produce **22** resulted in low yield and decreased *E* selectivity. Sulfone **21** was readily obtained from commercially available 1-phenyl-5-mercapto-1*H*-tetrazole (**20**) and *N*-(2-bromoethyl) phthalimide in 79% yield (2 steps). Deprotection of **22** with hydrazine accompanied complete removal of the 1-*tert*-butoxycarbonyl group and subsequent treatment with 4,5-dibromo-2-trichloroacetylpyrrole[15] afforded the protected oroidin derivative **24a** in 79% yield (2 steps). Final removal of the *tert*-butoxycarbonyl group under acidic conditions gave rise to oroidin (**1**) in 92% yield.[4a,6,16,17] In a similar manner, hymenidin (**2**)[18] was prepared from **23** by way of **24b**.[19] Spectral and physical properties of **1** and **2** were identical to those reported.[4a,6,17,20]

Finally, the synthesis of dispacamide (**3**) and monobromodispacamide (**4**) was examined starting with **22**. As shown in Scheme 5, catalytic reduction of **22** followed by deprotection with hydrazine and complete removal of the 1-*tert*-butoxycarbonyl group in the imidazole moiety gave amine **25** in 64% yield (3 steps). This was converted to **3** and **4** following the procedure reported by Horne et al.[21] with some modifications. Thus, after oxidation of **25** with tetra-*n*-butylammonium tribromide, the aliphatic primary amino group of the product was selectively protected with the *tert*-butoxycarbonyl group to simplify the purification, affording the 2-amino-Δ^1-imidazolin-4-one derivative **26** in 40% yield (2 steps). Sequential deprotection and acylation with the pyrrole derivatives[15,19] furnished dispacamide (**3**) and monobromodispacamide (**4**) both as an amorphous solids in 85% and 69% yields (2 steps), respectively.[22] Spectral data of **3** and **4** were in good agreement with those reported.[23]



Scheme 5 Total synthesis of dispacamide (**3**) and monobromodispacamide (**4**). *Reagents and conditions*: (a) H_2 (4 kg/cm^2), 10% Pd–C–EtOH, 50 °C, 13 h; (b) H_2NNH_2–EtOH, 50 °C,6 h; (c) 20% HCl–EtOH, r.t., overnight, 64% (3 steps from **22**); (d) tetra-*n*-butylammonium tribromide–DMSO, r.t., 1.5 h; (e) Boc_2O–MeOH, r.t., overnight, 40% (2 steps from **25**); (f) 20% HCl–EtOH, r.t., overnight; (g) 4,5-dibromo-2-trichloroacetylpyrrole or 4-bromo-2-trichloroacetylpyrrole, Na_2CO_3–DMF, r.t., overnight, 85% for **3** (2 steps from **26**), 69% for **4** (2 steps from **26**).

As described above, we have succeeded in exploring a novel synthetic route to 2-aminoimidazol-4-carbaldehyde derivatives **I**, the versatile synthetic intermediates for 2-aminoimidazole alkaloids, by featuring the reaction of *tert*-butoxycarbonylguanidine (**12a**) with 3-bromo-1,1-dimethoxymethylpropan-2-one (**10**) as a key step. Starting with 1-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminoimidazol-4-carbaldehyde (**19a**) thus obtained, expeditious synthesis of oroidin (**1**), hymenidin (**2**), dispacamide (**3**) and monobromodispacamide (**4**), the representative 2-aminoimidazole alkaloids, was accomplished, realizing the synthetic utility of **I**.

Acknowledgment

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(7) Physical and spectral data of the representative compounds. Compound **11**: amorphous solid. IR (KBr): 3295, 1686, 1625, 1113, 1052 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.02 (s, 3 H, Ac), 3.18 (s, 6 H, OMe), 5.24 [s, 1 H, $CH(OMe)_2$], 6.65 (s, 1 H, 4-CH), 11.08 (br s, 1 H, NHAc), 11.40 (br s, 1 H, 1-NH). LRMS (EI$^+$): *m/z* = 199 [M$^+$], 168, 126, 96. HRMS (EI$^+$): *m/z* calcd for $C_8H_{13}N_3O_3$: 199.0957; found: 199.0947. Compound **14a**: mp 134–136 °C (EtOAc). IR (KBr): 3463, 1740, 1637, 1342, 1121, 1060 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, *t*-Bu), 3.37 (s, 6 H, OMe), 5.27 [d, *J* = 1.2 Hz, 1 H, $CH(OMe)_2$], 5.56 (br s, 2 H, NH_2), 6.86 (d, *J* = 1.2 Hz, 1 H, 4-CH). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.0, 52.7, 85.0, 99.4, 109.3, 135.6, 149.4, 150.6. LRMS (EI$^+$): *m/z* = 257 [M$^+$], 226, 125, 96. Anal. Calcd for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.44; N, 16.33. Found: C, 51.20; H, 7.33; N, 16.36. Compound **16**: mp 156–158 °C (hexane–EtOAc). IR (KBr): 3417, 1736, 1640, 1372, 1358, 1127 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.57 (s, 9 H, *t*-Bu), 6.58 (br s, 2 H, NH_2), 7.21 (t, *J* = 7.3 Hz, 1 H, Ph), 7.33 (t, *J* = 7.3 Hz, 2 H, Ph), 7.33 (s, 1 H, 4-CH), 7.71 (d, *J* = 7.3 Hz, 2 H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.0, 85.1, 106.1, 125.0, 127.3, 128.5, 133.2, 137.7, 149.4, 150.8. LRMS (EI$^+$): *m/z* = 259 [M$^+$], 203, 159. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.72; H, 6.57; N, 16.21. Compound **18a**: mp 155–157 °C (dec.) (hexane–EtOAc). IR (KBr): 3409, 1711, 1648, 1604,

1170 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (s, 9 H, *t*-Bu), 7.49 (s, 1 H, 4-CH), 9.59 (s, 1 H, CHO). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.2, 82.6, 128.8, 137.6, 147.7, 153.1, 176.9. LRMS (EI$^+$): *m/z* = 211 [M$^+$], 155, 111. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.07; H, 6.11; N, 19.93. Compound **19a**: mp 112–114 °C (hexane–EtOAc). IR (KBr): 1755, 1697, 1532, 1305, 1152 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 9 H, *t*-Bu), 1.64 (s, 9 H, *t*-Bu), 7.70 (s, 1 H, 4-CH), 9.10 (br s, 1 H, BocNH), 9.92 (s, 1 H, CHO). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 27.8, 28.1, 82.5, 88.5, 117.2, 138.1, 142.8, 148.7, 149.6, 187.2. LRMS (EI$^+$): *m/z* = 311 [M$^+$], 211, 155, 111. Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 53.76; H, 6.63; N, 13.70.

(8) The reaction was continued until complete consumption of the starting material was ascertained by TLC analysis.

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(10) The crystallographic data was deposited at the Cambridge Crystallographic Data Centre. The deposition number is CCDC 605791.

(11) When the reaction of **15** and **12a** was examined in THF at 50 °C for 3 h (see below), **16** was obtained as an almost sole product in 68% yield along with a trace amount of **17**.

(12) To a solution of **12a** (478 mg, 3.0 mmol) in anhyd THF (3 mL) was added a solution of **10** (197 mg, 1.0 mmol) in anhyd THF (2 mL) under an argon atmosphere. After heating at 50 °C for 6 h, the solvent was removed in vacuo. Purification of the residue by column chromatography (SiO_2, EtOAc) afforded **14a** as a colorless solid (159 mg, 62%). An analytical sample of **14a** was prepared by recrystallization from EtOAc.

(13) We subjected **18a** to tritylation, acetylation, triisopropylsilylation and methoxymethylation under the standard reaction conditions. Although formation of the desired compounds corresponding to **19a** was observed in tritylation, acetylation and triisopropylsilylation, these products were found to be too unstable to be isolated in pure states. In the case of methoxymethylation, a complex mixture was obtained as the reaction product.

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