JOC*Article*

Total Synthesis of the Antiallergic Naphtho-α-pyrone Tetraglucoside, Cassiaside C_2, Isolated from Cassia Seeds

Zhaojun Zhang and Biao Yu*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

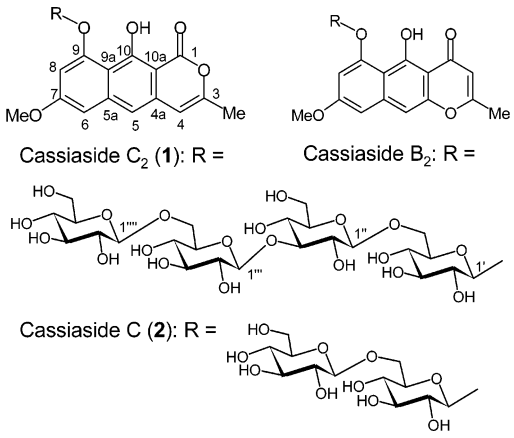
byu@pub.sioc.ac.cn

Received February 20, 2003

Toralactone 9-*O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl-(1→3)-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside (**1**, cassiaside C_2), isolated from *Cassia obtusifolia* L. and showing strong antiallergic activity, was concisely synthesized employing glycosyl trifluoroacetimidates as glycosylation agents. The unique naphtho-α-pyrone structure of toralactone (**5**) was constructed by condensation of orsellinate **8** with pyrone **9** in the presence of LDA as developed by Staunton and co-workers. The naphthol of toralactone showed minimal reactivity as an acceptor and was screened with various glycosyl donors. It is finally concluded that sacrifice of an excess amount of the trifluoroacetimidate or trichloroacetimidate donors (**6f**/**6g**, 6.0 equiv) in the presence of a catalytic amount of TMSOTf (0.05 and 0.3 equiv, respectively) afforded excellent yields of the coupling product, which was otherwise only a minor product under a variety of conditions examined.

Introduction

The seeds of *Cassia* plants are reputed in traditional Chinese medicine as vision-improving, antiasthenic, antihepatotoxic, and diuretic agents. Isolation of the chemical constituents from *Cassia obtusifolia* L. under the guidance of inhibition against histamine release from rat peritoneal mast cells induced by antigen−antibody reaction led to two novel naphthopyrone glycosides, cassiaside C_2 and cassiaside B_2.[1] They are isomers with an identical tetrasaccharide moiety, *O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl-(1→3)-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside. Cassiaside C_2 (**1**), the naphtho-α-pyrone (toralactone) tetraglucoside, showed a 53.9% inhibition at 10^{-4} M. Cassiaside B_2, the naphtho-*γ*-pyrone (rubrofusarin) counterpart, displayed 17.2% inhibition, and the potent antiinflammatory drug indomethacin showed 46.6% inhibition at 2.5×10^{-4} M.[1] From *Cassia* seeds, several shorter congeners have also been isolated, including toralactone gentiobioside (cassiaside C, **2**)[2,3,4a] and rubrofusarin gentiobioside.[2−4] The naphtho-α-pyrones, toralactone and its derivatives, have not been disclosed in any other natural sources. Attracted by the interesting bioactivities and the unique structure, and also with a purpose in mind to examine the utility of our newly developed glycosyl trifluoroacetimidates[5] for glycosylation, especially of the phenols, we set out to synthesize cassiaside C_2 (**1**) and herewith describe the results.



Results and Discussion

Cassiaside C_2 (**1**) consists of two synthetically distinct parts, the naphtho-α-pyrone (toralactone, **5**) and the tetraglucose. A convergent synthesis thus calls for a coupling of a tetraglucose derivative with the aglycon. However, glycosylation of a phenolic aglycon has long been recognized as a difficult task.[6] Completion of the total synthesis of vancomycin[7,8] and olivomycin A[9] rep-

* To whom correspondence should be addressed. Fax: (86)21-64166128.

(1) Kitanaka, S.; Nakayama, T.; Shibano, T.; Ohkoshi, E.; Takido, M. *Chem. Pharm. Bull.* **1998**, *46*, 1650.

(2) Hatano, T.; Uebayashi, H.; Ito, H.; Shiota, S.; Tsuchiya, T.; Yoshida, T.*Chem. Pharm. Bull.* **1999**, *47*, 1121.

(3) Kitanaka, S.; Takido, M. *Chem. Pharm. Bull.* **1988**, *36*, 3980.

(4) (a) Wong, S.-M.; Wong, M. M.; Seligmann, O.; Wagner, H. *Planta Med.* **1989**, *55*, 276. (b) Kaneda, M.; Morishita, E.; Shibata, S. *Chem. Pharm. Bull.* **1969**, *17*, 458.

(5) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099.

(6) Jensen, K. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2219.

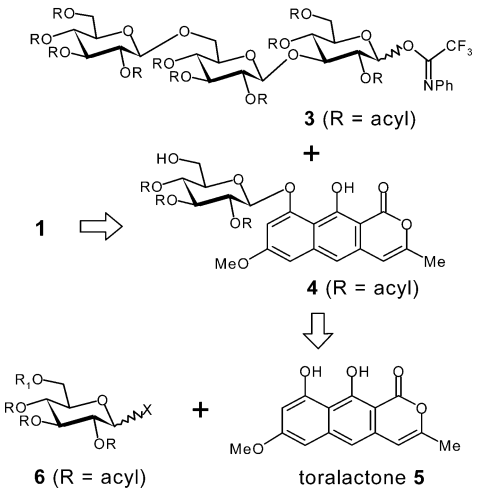
(7) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. Eur. J.* **1999**, *5*, 2648.

(8) Thompson, C.; Ge, M.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 1237.

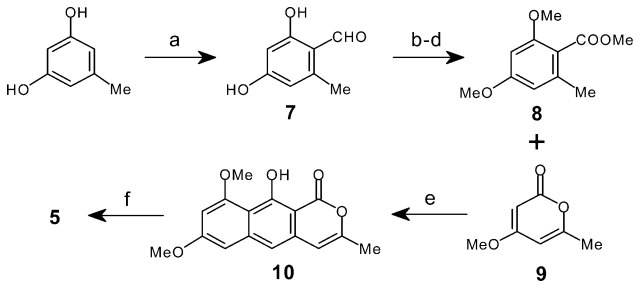
(9) (a) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990. (b) Roush, W. R.; Lin, X.-F.; *J. Am. Chem. Soc.* **1995**, *117*, 2236.

10.1021/jo034223u CCC: $25.00
Published on Web 07/08/2003

SCHEME 1. Synthetic Plan



SCHEME 2. Preparation of Toralactone 5[a]



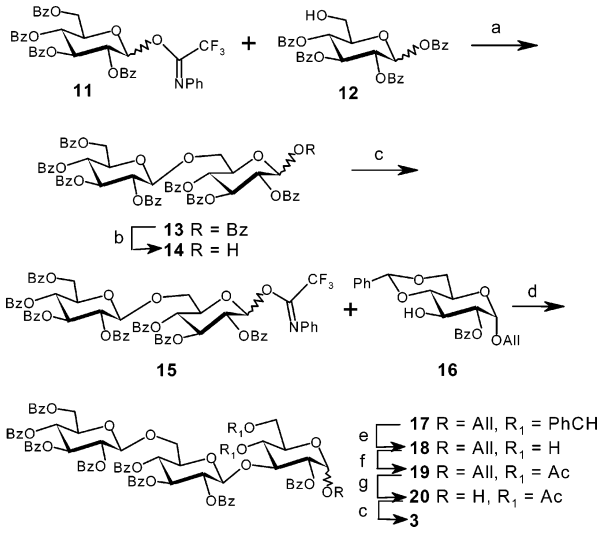
[a] Reagents and conditions: (a) DMF, $POCl_3$, 0 °C to rt; then 10% NaOH; then concd HCl, 80%; (b) MeI, K_2CO_3, acetone, 65 °C, 98%; (c) $NaClO_2$, NaH_2PO_4, DMSO, 10 °C to rt, 84%; (d) Me_2SO_4, NaOH, EtOH, reflux, 77%; (e) LDA (2.0 equiv), THF, −78 °C to rt; then 1 N HCl, 32%; (f) BBr_3, CH_2Cl_2, rt, 85%.

resents two formidable examples. Therefore, monosaccharide **4** was expected as the key intermediate for elaboration of the target molecule via coupling with trisaccharide donor **3** (Scheme 1). The glycosylation of toralactone (**5**) with monosaccharide donors (**6**), to afford **4**, thus turned out to be the crucial step in our synthesis. Extensive examination of the effectiveness of different glycosyl donors, especially of glycosyl trifluoroacetimidates, for this step was scheduled. Acyl groups were planned as protecting groups to ensure the stereoselective formation of the required β-D-glucopyranoside linkages and to leave ample choices for a distinguishable protective group on the 6-OH of **6**. Protection of the 10-OH of toralactone to ensure a regioselective 9-OH glycosylation was not considered since the 10-OH moiety, besides its stereohindrance, is hydrogen-bonded with the 1-carbonyl oxygen, with its ^{1}H NMR signal at a downfield of 13.55 ppm (for toralactone **5**) or 12.58 ppm (for **1**).

Toralactone **5** was readily prepared as shown in Scheme 2. Formylation of 3,5-dihydroxytoluene with DMF/$POCl_3$ gave 2,4-dihydroxy-6-methyl benzaldehyde (**7**, 80%).[10] After methylation of the phenols with methyl iodide, the aldehyde was oxidized with sodium chlorite to give the resulting carboxylic acid, which was then methylated with dimethyl sulfate to provide methyl

(10) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664.

SCHEME 3. Preparation of Trisaccharide Trifluoroacetimidate 3[a]



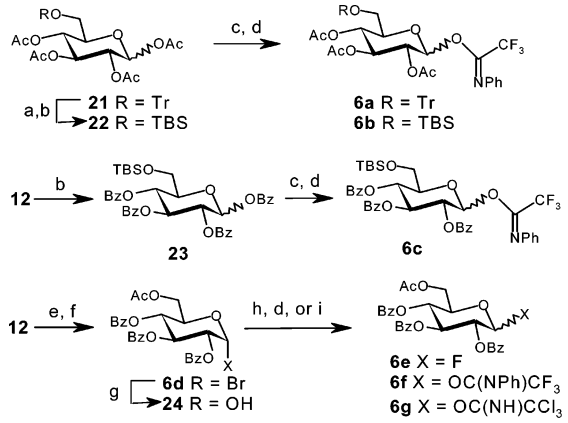
[a] Reagents and conditions: (a) TMSOTf (0.05 equiv), CH_2Cl_2, 4Å MS, rt, 98%; (b) NH_3, THF/MeOH (7:3), 0 °C to rt, 67%; (c) PhN=CClCF$_3$, K_2CO_3, acetone, rt, 99% for **15**, 87% for **3**; (d) TMSOTf (0.12 equiv), CH_2Cl_2, 4Å MS, rt, 86%; (e) 80% HOAc, 70 °C, 78%; (f) Ac_2O, pyridine, 65 °C, 97%; (g) $PdCl_2$, CH_2Cl_2/MeOH, rt, 89%.

orsellinate dimethyl ether **8** in a satisfactory yield (63% for three steps).[11] Pyrone **9** was prepared by methylation of 6-methyl-2,4-pyronone with dimethyl sulfate.[12] Coupling of orsellinate derivatives with pyrones in the presence of LDA to prepare naphtho-α-pyrones has been established by Staunton and co-workers.[13] Thus, treatment of **8** with LDA (2.0 equiv) followed by addition of pyrone **9** at −78 °C, warming to room temperature, and subjection to an acidic workup afforded the desired 9-*O*-methyl-toralactone **10** in 32% yield, which is comparable with the literature yields.[13,14] Selective removal of the 9-*O*-methyl group on **10** has been realized by Barbier et al.[14] However, we found the literature conditions (1 equiv of BBr_3, CH_2Cl_2, 30 min at −10 °C, then 1 h at 20 °C, 54%) needed to be modified (1.2 equiv of BBr_3, CH_2Cl_2, 6 h at rt) to force a clean reaction, providing toralactone **5** in 85% yield.

Preparation of the acyl-protected trisaccharide trifluoroacetimidate **3** was straightforward (Scheme 3). Glycosylation of the 6-OH of glucose tetrabenzoate **12**[15] with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate (**11**)[5b] under the standardized conditions (0.05 equiv of TMSOTf, CH_2Cl_2, 4 Å MS, rt)[5] gave disaccharide **13** in 98% yield. Selective removal of the anomeric benzoate on **13** with NH_3 in methanol provided **14** (67%),[16] which was then treated with *N*-phenyltrifluoroacetimidoyl chloride in the presence of K_2CO_3 in acetone to afford the

(11) Solladie, G.; Rubio, A.; Carreno, M. C.; Ruano, J. L. G. *Tetrahedron*: *Asymmetry* **1990**, *1*, 187.
(12) Nakata, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1693.
(13) (a) Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 205. (b) Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1043. (c) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1053.
(14) Parisot, D.; Devys, M.; Barbier, M. *J. Antibiot.* **1992**, *45*, 1799.
(15) Kovac, P.; Glaudemans, C. P. J. *J. Carbohydr. Chem.* **1988**, *7*, 317.

SCHEME 4. Preparation of Donors 6a−g[a]

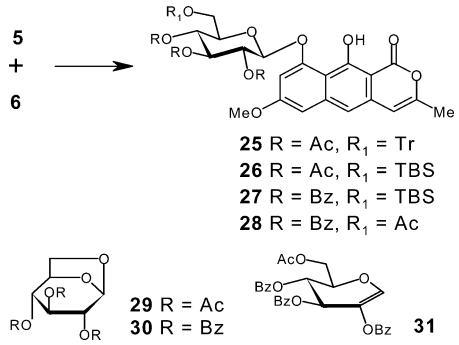


[a] Reagents and conditions: (a) 90% CF_3COOH, 0 °C to rt, 77%; (b) TBSCl, imidazole, DMF, rt, 86% for **22**, 88% for **23**; (c) NH_3, THF/MeOH, rt; (d) PhN=$CClCF_3$, K_2CO_3, acetone, rt, 74% for **6a** (two steps), 62% for **6b** (two steps), 86% for **6c** (two steps), 97% for **6f**; (e) Ac_2O, pyridine, rt; (f) 33% HBr/HOAc, CH_2Cl_2, rt, 80% (two steps); (g) Ag_2CO_3 (1.5 equiv), acetone/H_2O, rt, 98%; (h) DAST, THF, −30 °C to rt, 86%; (i) CCl_3CN, K_2CO_3, acetone, rt, 90%.

disaccharide trifluoroacetimidate **15** (99%). Coupling of **15** with the hindered 3-OH of allyl glucoside **16**[17] gave a satisfactory yield of the expected trisaccharide **17** (86%) when a slightly increased amount of TMSOTf (0.12 equiv) was employed. Cleavage of the anomeric allyl group in the presence of a labile 4,6-*O*-benzylidene was viewed as potentially problematic.[18] Furthermore, synchronization of the protective groups at an earlier stage would facilitate the final deprotection. Therefore, the 4,6-*O*-benzylidene on **17** was removed with 80% HOAc to give diol **18** (78%), which was then subjected to protection with acetates. Acetylation of **18** with Ac_2O in pyridine at ambient temperature did not complete for 22 h; 4,6-di-*O*-acetate **19** was isolated in 73% yield along with another product, which was identified as the 6-*O*-acetate.[19] Thus, forced conditions (65 °C, overnight) were used, producing **19** in an excellent yield (97%). Removal of the anomeric allyl group on **19** was then realized by treatment with $PdCl_2$ in methanol,[20] affording **20** in 89% yield, which was then converted readily to the trisaccharide trifluoroacetimidate **3** (87%) under the standardized conditions (PhN=$CClCF_3$, K_2CO_3, acetone, rt).

Glucopyranosyl donors **6a−g** utilized in the coupling experiments with toralactone **5** were prepared as shown in Scheme 4. These donors contain acetyl or benzoyl groups on the 2,3,4-OHs and a protective group capable of being selective removed from the 6-OH (Tr, TBS, or Ac). 1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-D-glucopyranoside **21**[21] was treated with 90% CF_3COOH to release the 6-OH,[22] which was then protected with a *tert*-butyldimethylsilyl (TBS) ether to give **22**.[23] Protection of the 6-OH of **12** with a TBS ether provided 1,2,3,4-tetra-*O*-benzoyl-6-*O*-TBS-D-glucopyranoside **23**. Compounds **21**−**23** were then subjected to the common operations, i.e., selective removal of the anomeric acetate or benzoate (NH_3, THF/MeOH, 0 °C) and addition with *N*-phenyl trifluoroacetimidoyl chloride (K_2CO_3, acetone, rt), to provide glycosyl trifluoroacetimidates **6a−c** in satisfactory yields. 6-*O*-Acetyl-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl bromide (**6d**), prepared from **12**,[24] was converted into 1-OH sugar **24** under the action of Ag_2CO_3 in aqueous acetone, which was then transformed readily into fluoride **6e** (DAST, THF),[25] trifluoroacetimidate **6f**, and trichloroacetimidate **6g** under usual conditions.

SCHEME 5. Glycosylation of Toralactone 5 with Donors 6a−g



We started with 2,3,4-tri-*O*-acetyl-6-*O*-trityl-D-glucopyranosyl trifluoroacetimidate **6a** to explore the glycosylation of toralactone **5** (Scheme 5). Chlorobenzene, besides the common methylene chloride and ethylene dichloride, was also tried as the reaction solvent due to its better solubility for **5**. Only a trace amount of the putative coupling product was detected under the promotion of TMSOTf (0.3 equiv) at ambient temperature (Table 1, entry 1). Suzuki et al. have reported that the nucleophilicity of a naphthol could be increased in the presence of a hindered base (2,6-di-*tert*-butyl-4-methylpyridine, DTBMP) so as to facilitate the glycosylation reaction.[8,26] Thus, TMSOTf (1.5 equiv) and DTBMP (2.5 equiv) were used to promote the coupling reaction, affording the desired product **25** in 24% yield (Table 1, entry 2). It was encouraging that only the 9-OH of the diol **5** was glycosylated and only the desired β-anomeric product (**25**) was generated, as indicated by the appearance of a broad ^{1}H NMR signal at 12.70 ppm for 10-OH and a doublet (J = 7.5 Hz) at 5.47 ppm for the anomeric H-1′. However, because a considerable amount of the 6-*O*-trityl group was found to be released under the above glycosylation conditions, we turned our attention to donor **6b**, which bears a 6-*O*-TBS group, for glycosylation of **5**. Unfortunately, under the normal glycosylation conditions for glycosyl trifluoroacetimidates/trichloroacetimidates (Table 1, entries 3−4), the desired coupling product **26** was produced in only trace amounts; meanwhile, most of the donor **6b** was converted into 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose **29**.[27] Similarly, glycosylation of **5**

(16) Pelyvas, I.; Lindhorst, T.; Thiem, J. *Liebigs Ann. Chem.* **1990**, 761.
(17) Fiandor, J.; Garcia-Lopez, M. T.; Heras, F. G.; Mendez-Castrillon, P. P. *Synthesis* **1985**, *12*, 1121.
(18) Yu, B.; Zhang, J.; Lu, S.; Hui, Y. *Synlett* **1998**, 29.
(19) Mulard, L. A.; Ughetto-Monfrin, J. *J. Carbohydr. Chem.* **2000**, *19*, 193.
(20) Ogawa, T.; Yamamoto, H. *Agric. Biol. Chem.* **1985**, *49*, 475.
(21) Utamura, T.; Kuromatsu, K.; Suwa, K.; Koizumi, K.; Shingu, T. *Bull. Chem. Soc.* **1986**, *34*, 2341.
(22) Lee, R. T.; Lee, Y. C. *Carbohydr. Res.* **1982**, *101*, 39.
(23) Beagley, B.; Larsen, D. S.; Pritchard, R. G.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3113.
(24) Konda, Y.; Iwasaki, Y.; Takahata, S.; Arima, S.; Toida, T.; Kaji, E.; Takeda, K.; Harigaya, Y. *Chem. Pharm. Bull.* **1997**, *45*, 626.
(25) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.
(26) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1994**, *35*, 4591.

TABLE 1. Glycosylation of Toralactone 5 with Donors 6a−g

entry	donor (equiv)	conditions[a]	products (yield, %)
1	**6a** (1.2)	TMSOTf (0.3 equiv), PhCl, rt, 2 h	**25** (trace)
2		TMSOTf (1.5 equiv), DTBMP (2.5 equiv), PhCl, rt, 15 h	**25** (<25)
3	**6b** (1.4)	TMSOTf (0.2 equiv), $ClCH_2CH_2Cl$, rt, 24 h	**26** (trace), **29**
4		$BF_3{\cdot}OEt_2$ (0.2−3.4 equiv), $ClCH_2CH_2Cl$, −78 °C to rt, 16 h	**26** (no), **29**
5	**6c** (1.5)	TMSOTf (0.2 equiv), CH_2Cl_2, 0 °C to rt, 2 h;	**27** (trace)
		additional TMSOTf (0.6 equiv) was added, rt, 24 h	**27** (trace), **30**
6	**6d** (3.0)	TBAB (1.2 equiv), borate buffer (pH = 10.8), $CHCl_3$, 52 °C, 12 h	**28** (<20)
7	(1.5)	TBAB (1.2 equiv), 0.06 M K_2CO_3, $CHCl_3$, 40 °C, 24 h	**28** (trace)
8	(2.0)	$CdCO_3$ (4.0 equiv), toluene, reflux, 19 h	complex
9	**6e** (3.0)	$BF_3{\cdot}OEt_2$ (3.0−20.0 equiv), DTBMP (4.0 equiv), CH_2Cl_2, rt, 30 h	**28** (no)
10	**6f** (1.5)	TMSOTf (0.6 equiv), CH_2Cl_2, 0−25 °C, 5 h	**28** (<10), **31**
11	(1.5)	TMSOTf (1.0 equiv), DTBMP (1.2 equiv), CH_2Cl_2, 0−25 °C, 9 h	**28** (28), **31**
12	(6.0)	TMSOTf (1.0 equiv), DTBMP (1.2 equiv), CH_2Cl_2, 0−25 °C, 9 h	**28** (90), **31**
13	(6.0)	TMSOTf (0.05 equiv), CH_2Cl_2, 0−25 °C, 14 h	**28** (90), **31**
14	**6g** (2.0)	TMSOTf (0.1 equiv), CH_2Cl_2, 0 °C to rt, 23 h	**28** (33)
15	(6.0)	TMSOTf (0.1 equiv), CH_2Cl_2, 0 °C to rt, 23 h;	**28** (<40)
		additional TMSOTf (0.2 equiv) was added, 4 h	**28** (82)

[a] All reactions were carried out in the presence of 4 Å MS and a positive pressure of argon.

with 2,3,4-tri-*O*-Bz-6-*O*-TBS-D-glucopyranosyl trifluoroacetimidate **6c** met with no success; the intramolecular glycosidation with cleavage of the 6-*O*-TBS group readily took place, producing 1,6-anhydro-2,3,4-tri-*O*-benzoyl-*β*-D-glucopyranose **30**[28] as the major product (Table 1, entry 5). Therefore, a more robust protective group on the 6-OH of the donor **6** is mandatory to achieve an effective glycosylation of naphthol **5**, which shows minimal nucleophilicity.

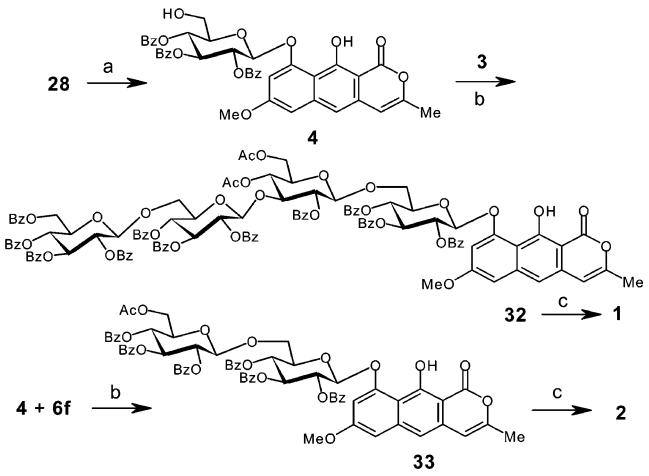
Our attention was then focused on the 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-D-glucopyranosyl donors **6d**−**g**. The most frequently employed protocol for glycosylation of phenols relies on the S_N2 displacement of the anomeric bromide with phenolates generated in basic conditions.[6,29] However, attempted coupling of toralactone **5** with glycosyl bromide **6d** under literature conditions, including the use of tetrabutylammonium bromide (TBAB) as a phase-transfer reagent[29a−c] and the use of $CdCO_3$ as a base,[24,29d,e] all failed to give considerable yields of the desired product **28** (Table 1, entries 6−8). Peracetylglucosyl fluoride under the action of $BF_3{\cdot}OEt_2$ and DTBMP has been reported as a successful protocol for glycosylation of phenols.[30] However, applying the literature conditions to the coupling of **5** with glycosyl fluoride **6e** gave no desired **28** (Table 1, entry 9).

Our last resort was the use of 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate **6f** as the donor for glycosylation of toralactone **5**. We expect that it would give an increased yield of the coupling product from donor **6a** bearing a labile 6-*O*-trityl group. However, under conditions similar to those for the coupling of **6a** with **5** (Table 1, entries 10 and 11), glycosylation of **5** with **6f** did not improve the coupling yield. In addition, trifluoroacetimidate **6f** was found to be eliminated into glucal **31**[24] mainly. Attempts to modify the reaction conditions, such as TMSOTf or $BF_3{\cdot}OEt_2$ equivalents, "inverse" addition sequence,[31] as well as concentration and temperature, led to no appreciable improvement. Finally, we proposed that employing a large excess amount of the donor **6f** in the reaction would give a higher yield of the coupling product **28**, if trifluoroacetimidate **6f**, which readily underwent elimination, could still provide enough of the glycosyl oxacarbenium intermediate over a sufficient period for consumption of naphthol **5**. To our delight, applying 6.0 equiv of **6f** to the previous coupling conditions (1.0 equiv of TMSOTf, 1.2 equiv of DTBMP, 4 Å MS, CH_2Cl_2, 0−25 °C) generated **28** in a remarkable 90% yield (Table 1, entry 12). The presumed role of DTBMP, to activate the phenolic O−H bond, thus enhancing the nucleophilicity of the oxygen, was not consistent with the observation that addition of DTBMP into **5** did not change the ^1H NMR chemical shifts of 9-OH and 10-OH. In addition, when we did not add DTBMP and decreased the amount of TMSOTf to 0.05 equiv, i.e., the previous typical glycosylation conditions for glycosyl trifluoroacetimidate,[5] coupling of **5** with 6.0 equiv of **6f** afforded **28** in 90% yield (Table 1, entry 13). In comparison, we also tried the trichloroacetimidate counterpart **6g** for glycosylation of **5**. Similar results as glycosylation with trifluoroacetimidate donor **6f** were obtained (Table 1, entries 14 and 15). The obvious difference noticed was that trichloroacetimidate **6g** did not undergo ready elimination to produce glucal **31**, but instead predominantly generated the corresponding 1-OH derivative.

With the toralactone glucoside **28** being successfully prepared, the completion of the synthesis of Cassiaside C_2 is straightforward (Scheme 6). The primary 6-*O*-acetate on **28** was selectively removed with 1% HCl in $MeOH/CH_2Cl_2$ (85%), which was then coupled with the trisaccharide trifluoroacetimidate **3** under the usual conditions (0.1 equiv of TMSOTf, 4 Å MS, CH_2Cl_2, 0 °C to rt) to provide the tetrasaccharide **32** in a satisfactory 73% yield. Finally, removal of the acetate and benzoate groups on **32** in the presence of K_2CO_3 in MeOH/THF (3:2) at room temperature afforded the target molecule

(27) Oikawa, M.; Shintaku, T.; Sekljic, H.; Fukase, K.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1857.
(28) Ohrui, H.; Horiki, H.; Kishi, H.; Meguro, H. *Agric. Biol. Chem.* **1983**, *47*, 1101.
(29) (a) Grabley, S.; Gareis, M.; Böckers, W.; Thiem, J. *Synthesis.* **1992**, 1078. (b) Dess, D.; Kleine, H. P.; Weinberg, D. V.; Kaufman, R. J.; Sidhu, R. S. *Synthesis* **1981**, 883. (c) Li, M.; Han, X.; Yu, B. *Tetrahedron Lett.* **2002**, *43*, 9467. (d) Tsujihara, K.; Hongo, M.; Saito, K.; Inamasu, M.; Arakawa, K.; Oku, A.; Matsumoto, M. *Chem. Pharm. Bull.* **1996**, *44*, 1174. (e) Dick, W. E., Jr. *Carbohydr. Res.* **1979**, *70*, 313.
(30) Oyama, K.-I.; Kondo, T. *Synlett* **1999**, 1627.
(31) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353.

SCHEME 6. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) 1% HCl, MeOH/CH_2Cl_2, rt, 85%; (b) **3** (0.8 equiv) or **6f** (1.2 equiv), TMSOTf (0.1 equiv), 4Å MS, CH_2Cl_2, 0 °C to rt, 73% for **32**, 92% for **33**; (c) K_2CO_3, MeOH/THF (3:2), rt; then Dowex H^+ resin, 85% for **1**, 97% for **2**.

1 cleanly, which was further purified by C-18 reversed-phase column chromatography (85%).

The diagnostic ^1H NMR signals of **1** are identical to those reported by Kitanaka et al.,[1] including the four anomeric hydrogens and those on the toralactone aglycon. The ^{13}C NMR signals of **1** are in good accordance with those listed in the literature,[1] except for the absence of a signal at 168.2 ppm, which was assigned to C-10a by the authors, and the presence of a signal at 98.9 ppm.[32] The optical rotation value of **1** was measured to be $[\alpha]^{18}_D = -29.6$ (*c* 0.8, H_2O).[33] Incidentally, the short congener of **1**, cassiaside C (**2**), was synthesized from **28** (Scheme 6) and the characterizing data was consistent with data reported by three groups,[2,3,4a] including optical rotation data. We conclude that our synthesis of cassiaside C_2 (**1**) is complete and the structure correct.

(32) This is an appropriate chemical shift for C-10a and 168.2 ppm is not, an observation supported by the same authors in their assignments for toralactone glycoside **2**.[3]

(33) The optical rotation data for cassiaside B_2 has been questioned by Yoshida et al.,[2] and we raise the same issue with that reported in the same publication for **1**.

Conclusion

Toralactone 9-*O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl-(1→3)-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside (**1**), claimed by Kitanaka et al. to be isolated from *Cassia obtusifolia* L. and possess strong antiallergic activity, was concisely synthesized employing glycosyl trifluoroacetimidates as donors. The glycosylation of the naphthol, toralactone, was intensively screened against a variety of conditions. It was concluded that sacrifice of an excess amount of the trifluoroacetimidate or trichloroacetimidate donors (6.0 equiv) in the presence of a catalytic amount of TMSOTf (0.05 and 0.3 equiv, respectively) was able to afford excellent yields of the coupling product, which was otherwise only a minor product under other conditions examined. This protocol might render a useful alternative for the construction of the glycosidic linkages with alcohols which are difficult for glycosylation.

Acknowledgment. The work described in the paper was supported by the National Natural Science Foundation of China (20172068, 29925203), the Committee of Science and Technology of Shanghai (01JC14053), and the Area of Excellence Scheme established under the University Grants Committee of Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01).

Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**6**(**a**−**g**), **10**, **13**−**15**, **17**−**20**, **23**, **24**, **28**, **32**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034223U