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Efficient Syntheses of Novel C2′-Alkylated (±)-K252a Analogues

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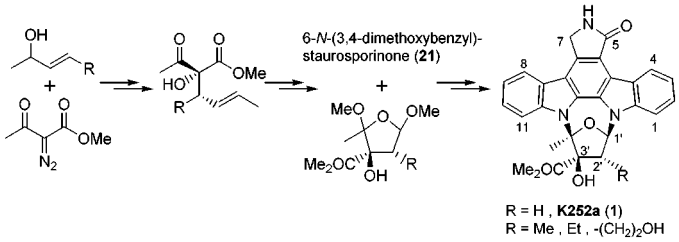
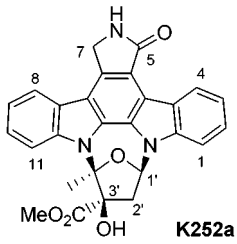
ABSTRACT



Recent efforts in our laboratories have resulted in a synthetic approach toward C2′-alkylated K252a analogues via extension of a K252a cyclofuranosylation strategy. The bis-indole-*N*-glycosidic coupling of 6-*N*-(3,4-dimethoxybenzyl)-staurosporinone (21) with a number of highly functionalized carbohydrates has given access to previously unattainable, biologically relevant analogues.

K252a (**1**), isolated originally from the culture broth of *Actinomadura* by Sezaki[1] and later isolated from *Nocardiopsis* by Kase in a screen for antagonists of Ca^{2+}-mediated



K252a (1)

signaling, is a potent PKC inhibitor.[2] In addition, K252a is considered a promising lead compound in the search for therapeutic agents against cancer and several neurodegenerative diseases.[3,4] Consequently, a number of derivatization studies have been initiated both academically and industrially.[5]

Strategies based on alteration of natural material have been fruitful, producing numerous analogues resulting from acylation/alkylation of the amide nitrogen, modification of the aromatic moieties (C3 and/or C9), oxidation at C7, as well as modification of the carbohydrate via transesterification, saponification/amidation, reduction of the methyl ester, and

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(1) Sezaki, M.; Sasaki, T.; Nakazawa; T., Takeda, U.; Iwata, M.; Watanabe, T.; Koyama, M.; Kai, F.; Shomura, T.; Kojima, M. *J. Antibiot.* **1985**, *38*, 1437.

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(3) (a) Chin, L. S.; Murray, S. F.; Doherty, P. F.; Singh S. K. *Cancer Invest.* **1999**, *17*, 391. (b) Delsite, R.; Djakiew, D. *J. Androl.* **1996**, *17*, 481. (c) Nakayama, T.; Hashimoto, Y.; Kaneko, Y.; Kurokawa, K. *Biochem. Biophys. Res. Commun.* **1996**, *224*, 180.

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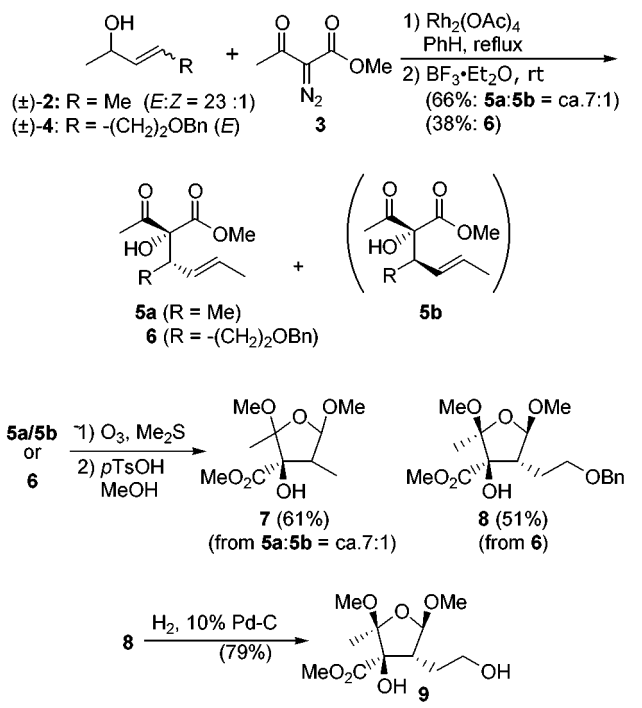
alkylation of the tertiary alcohol. However, exploration of the chemical space surrounding the furanose methylene (C2′) and the lactam methylene (C7) has been severely limited by the lack of an efficient synthetic route. Recently, we reported an efficient, convergent synthesis of K252a[6,7] and later extended our methodology to access C7 substituted K252a analogues.[5,8] The success of these previous endeavors led us to explore the potential for manipulation of the K252a carbohydrate. Herein we report facile synthetic access to C2′-alkylated K252a carbohydrates, as well as the preparation of a new class of K252a analogues via acid-promoted cyclofuranosylation of these novel carbohydrates with 6-*N*-(3,4-dimethoxybenzyl)-staurosporinone (**21**).[6,9]

Initially we sought to extend our K252a carbohydrate synthesis by stereoselectively accessing a C2′-methyl furanose as shown in Scheme 1. Diazo ester **3** and commercial

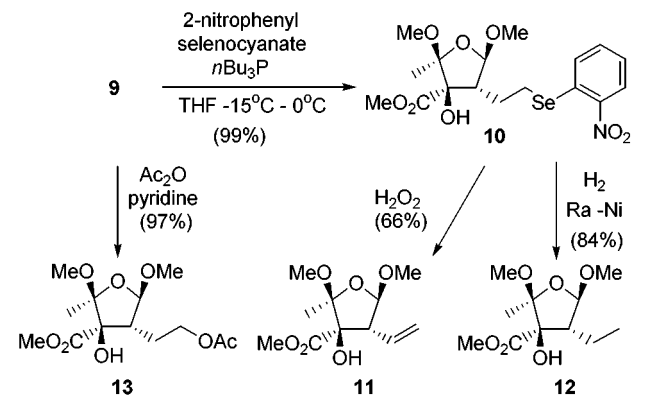
Scheme 1



(±)-3-penten-2-ol (**2**) (*E*:*Z* = 23:1) were subjected to our one-pot tandem [3,3]/[1,2] rearrangement protocol.[6,10] Thus, rhodium-carbenoid initiated Claisen rearrangement followed by a BF_3•OEt_2-promoted 1,2 alkyl shift smoothly gave approximately a 7:1 mixture of **5a**:**5b**.[11] Ozonolysis and acid-promoted cyclization gave a diastereomeric mixture of furanoses **7** in 61% yield. After flash chromatography the major diastereomer (27% overall yield) was isolated and utilized for all further cyclofuranosylation studies. Confident our strategy was amenable to preparation of C2′-alkyl derivatives, we set out to carry functionalized allylic alcohols through the same series to yield carbohydrates bearing a handle for subsequent manipulation. We were pleased to find that our established procedure was tolerant of the benzyloxyethyl functionality; thus, known allylic alcohol (±)-**4**[12] combined with **3** to smoothly afford **6**. Subsequent ozonolysis and acid-promoted cyclization gave carbohydrate **8** as a single diastereomer. Hydrogenolysis of **8** cleanly afforded **9**, whose relative stereochemistry was confirmed by X-ray crystallographic analysis.[13]

Conversion of **9** to **10** according to Grieco's procedure[14] set the stage for the preparation of cyclofuranosylation precursors **11** and **12** by oxidation−elimination[15] and reduction,[16] respectively. Additionally, **13** could be accessed directly by acetylation of **9** (Scheme 2).

Scheme 2



With several furanosylation precursors in hand, we examined cyclofuranosylation using model aglycon **14** as a coupling partner.[17] We were delighted to find that the various carbohydrates underwent cyclofuranosylation in good to

(6) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J., Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641.

(7) For alternate syntheses see: Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501 and ref 9c.

(8) Wood, J. L.; Petsch, D. T.; Stoltz, B. M.; Hawkins, E. M.; Elbaum, D.; Stover, D. R. *Synthesis* **1999**, 1529.

(9) Several groups including our own have developed protocols for the acid-catalyzed furanosylation of an indolocarbazole nucleus using C2′ unsubstituted carbohydrate moieties. (a) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309. (b) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirschmeier, P.; Lin, S.-I.; Petrin, J.; Rosinski, K.; Shankar, B. B.; Wilson, O. *Bioorg. Med. Chem. Lett.* **1993**. *3*, 1537. (c) Lowinger, T. B.; Chu, J.; Spence, P. L. *Tetrahedron Lett.* **1995**, *36*, 8383.

(10) For the rhodium-carbenoid initiated Claisen rearrangement, see: (a) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748. (b) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371.

(11) We anticipated that the major isomer **5a** would be consistent with our previous stereochemical observations, i.e., would arise from a chairlike Claisen transition state (Z-enol) followed by a syn-periplanar relationship between the hydroxyl and carbonyl oxygens in the reactive conformer for the 1,2 alkyl shift.[6,10]

(12) Belval, F.; Fruchier, A.; Chavis, C.; Montero, J.-L.; Lucas, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 697.

(13) We found that our stereochemical assignment of **6** was correct as **9** possessed the anticipated relative configuration between C2′ and C3′ (numbering based on K252a carbohydrate).

(14) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

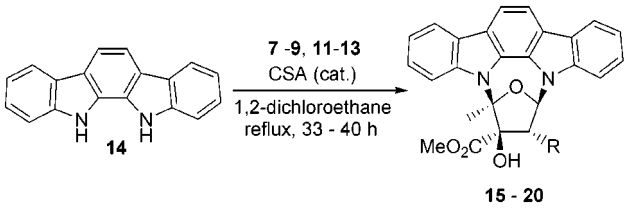
(15) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.

(16) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51.

(17) Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652.

excellent yield, giving a single diastereomer in all cases (Table 1, entries 1−5).[18]

Table 1. Model Cyclofuranosylation Studies



entry	carbohydrate (equiv)	product	yield
1	**7** (3.4)[a]	**15** (R = methyl)	89%
2	**12** (2.0)	**16** (R = ethyl)	94%
3	**11** (2.0)	**17** (R = vinyl)	55%
4	**8** (2.0)	**18** (R = $-(CH_2)_2OBn$)	45%
5	**13** (2.0)	**19** (R = $-(CH_2)_2OAc$)	83%
6	**9** (2.0)	**20** (R = $-(CH_2)_2OH$)	*b*

[a] Carbohydrate was added over 16 h. [b] Intractable mixture, **20** not isolable.

Crystallographic analyses of **15** and **16** (Figure 1) confirmed that the cyclofuranosylation proceeds with the

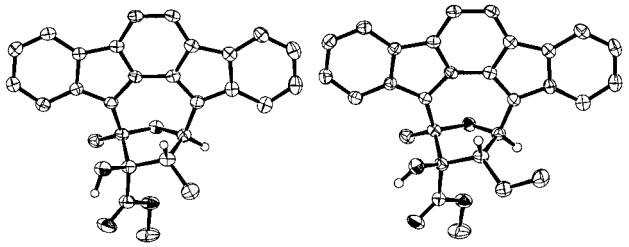


Figure 1. ORTEP plot of **15** (left) and **16** (right).

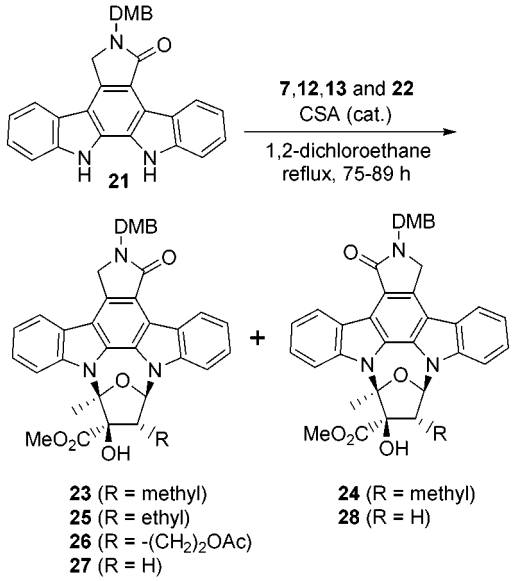
anticipated facial selectivity and that **15** possesses the correct C2′−C3′ relative stereochemistry.[19] Interestingly, we have not observed a cyclofuranosylation product possessing an anti relationship between the indolocarbozole and C3′-hydroxyl.

Having established feasibility with a model aglycon, we turned toward coupling **7**, **12**, and **13** with **21**.[6] As shown in Table 2, **21** was treated with **7**, **12**, and **13** under our established reaction conditions (CSA, 1,2-dichloroethane, reflux).[6,8] Cyclofuranosylation of **7** proceeds in reasonable yield (entry 1) compared to that of the K252a carbohydrate (entry 5). However, despite similar reactivity of **7**, **12**, and

(18) A considerable amount of benzylated **14** (at both indole nitrogens and as a mixture around the aromatic rings) was detected, accounting for the reduced yields when using **8**.

(19) Further, **17**−**19** were rigorously chemically correlated to **16**. The chemical correlation parallels the furanose interconversions illustrated in Scheme 1 and is detailed in the Supporting Information.

Table 2. Cyclofuranosylation with **21**



entry	carbohydrate[a] (equiv)	yield[b] (product)
1	**7** (2.2)	40% (**23**), 9% (**24**)
2[c]	**12** (2.2)	22% (**25**)
3	**13** (2.2)	11% (**26**)
4	**13** (3.5)	19% (**26**)
5[d]	**22** (2.0)	53% (**27**), 27% (**28**)

[a] Carbohydrate was added over 24 h. [b] Isolated yield. [c] Unnatural regioisomer was detectable in the crude reaction mixture but was not isolable in this case. [d] See ref 6, **22** is K252a carbohydrate.

13 in the model system, we found the cyclofuranosylation of **12** and **13** with **21** to be extremely sluggish. Isolable

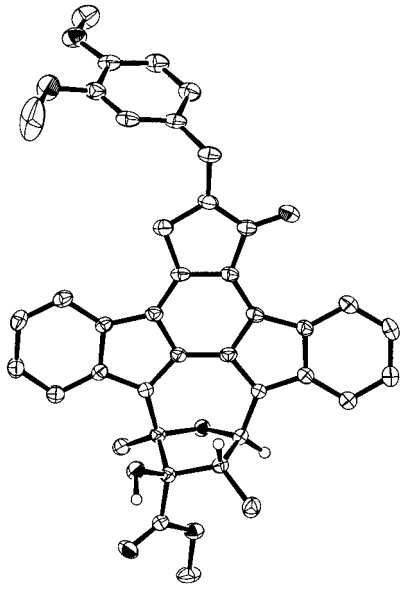
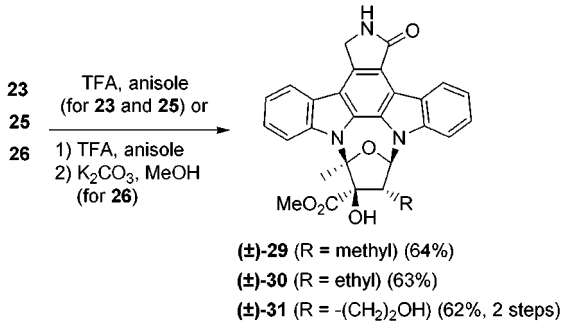


Figure 2. ORTEP plot of **23**.

cyclized products diminished greatly with increasing size of the C2′-substituent. Subsequent preparation of **25** and **26** proceeded with only modest success (entries 2 and 3). Efforts to improve the yield by altering stoichiometry were met with limited success (entry 4). Stereochemical assignments for **23**−**26** are based on the analogous model system products. Further, the regiochemistry for **23**−**26** were based on analogy between characteristic ^{1}H chemical shifts in the aromatic region of **27** and its unnatural regioisomer **28**. Crystallographic analysis of **23** (Figure 2) confirmed these assignments. Notably, there is improvement in the regioselectivity of the cyclofuranosylation with the introduction of a C2′-substituent. While cyclization of **22** gave a 2:1 mixture of natural to unnatural regioisomers, the ratio improved to 4:1 with the use of **7** as the carbohydrate.

Final deprotection of **23**, **25**, and **26** (Scheme 3) using TFA in the presence of anisole (and deacylation with K_2CO_3/MeOH) proceeded without incident to afford **29**−**31** in reasonable yield. The analogues **29**−**31** represent a novel class of K252a derivatives readily available via our strategy.

Scheme 3



(±)-29 (R = methyl) (64%)
(±)-30 (R = ethyl) (63%)
(±)-31 (R = -$(CH_2)_2$OH) (62%, 2 steps)

With this novel group of K252a analogues in hand we briefly examined the affects of C2′ functionalization on the reported kinase specificity and inhibitory potency.[20] As illustrated in Table 3, modification at C2′ minimally reduces the activity of **29**−**31** against PKC, PAK, and PKA (a notable exception being the potency of **30** for PKC). However, in the case of the hydroxyethyl derivative **31** the selectivity for PKC inhibition against PKA and PAK inhibition improves about 2-fold (Table 3) as compared to natural K252a.

Table 3. IC_{50} Values and Selectivities for C2′-Alkylated K252a Analogues and K252a (Natural)

		IC_{50} (μM)			selectivity ratio	
	R	PKC	PKA	PAK	PKC:PKA	PKC:PAK
(±)-29	methyl	0.5	2	3	4:1	6:1
(±)-30	ethyl	4	6	4	1.5:1	1:1
(±)-31	−$(CH_2)_2$OH	0.1	4	4	40:1	40:1
K262a (natural)	H	0.05	0.8	1	16:1	20:1

In conclusion, we have demonstrated efficient access to a number of highly substituted cyclfuranosylation precursors suitable for the preparation of novel C2′-alkylated (±)-K252a derivatives. We are currently undertaking a systematic investigation of the biological relevance of this class of derivatives.

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Supporting Information Available: Experimental and spectral data pertaining to all new compounds and X-ray data for **9**, **15**, **16**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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