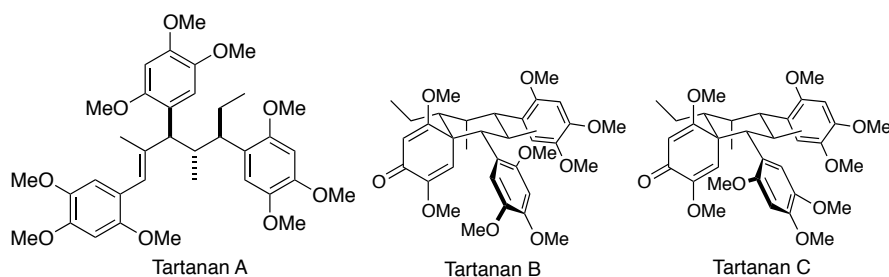


Tatanans A–C

Tatanans A, B and C have previously been reported to have potent glucokinase-activating properties that exceed the in vitro activity of known synthetic antidiabetic agents. Contrary to these reports, Zakarian by running assays utilizing pure recombinant human enzyme demonstrated that tatanans do not function as allosteric activators of glucokinase.

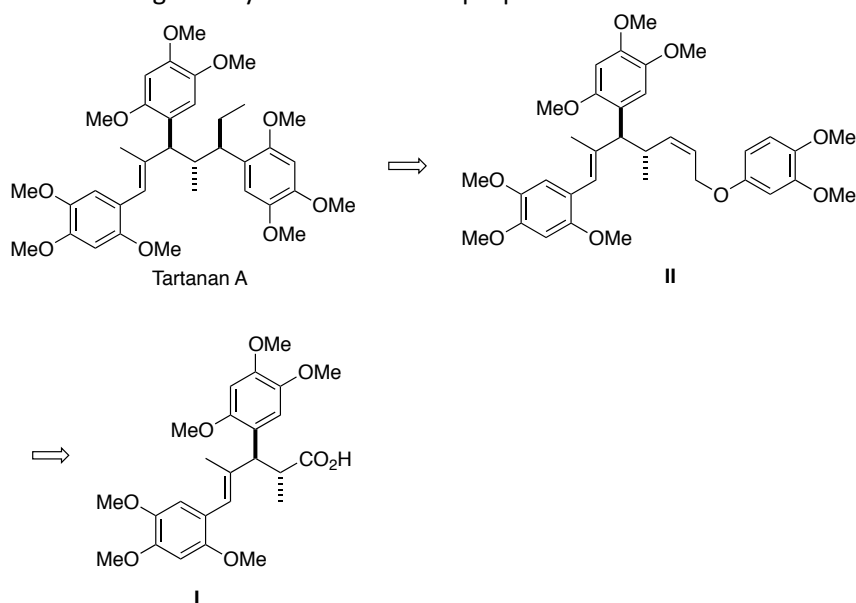


Biosynthesis

- 1) To which class of compounds belongs these these three natural products
- 2) What is the relation between tatanan B and C?
- 3) Give a plausible biosynthetic relationship between acyclic tatanan A and spirocyclic tatanans B and C

Synthesis

The following retrosynthesis has been proposed:



- 4) Propose a reaction sequence to convert II to tatanan A.
- 5) Propose a reaction sequence to convert I to II.
- 6) Propose a method to prepare I in optically pure form.

Reference: A. Zakarian et al. *Nat. Chem.* **2013**, *5*, 410.

Enantioselective synthesis of tatanans A–C and reinvestigation of their glucokinase-activating properties

Qing Xiao¹, Jeffrey J. Jackson¹, Ashok Basak¹, Joseph M. Bowler², Brian G. Miller^{2*} and Armen Zakarian^{1*}

The tatanans are members of a novel class of complex sesquilignan natural products recently isolated from the rhizomes of *Acorus tatarinowii* Schott plants. Tatanans A, B and C have previously been reported to have potent glucokinase-activating properties that exceed the *in vitro* activity of known synthetic antidiabetic agents. Here, using a series of sequential [3,3]-sigmatropic rearrangements, we report the total synthesis of tatanan A in 13 steps and 13% overall yield. We also complete a concise enantioselective total synthesis of more complex, atropisomeric tatanans B and C via a distinct convergent strategy based on a palladium-catalysed diastereotopic aromatic group differentiation (12 steps, 4% and 8% overall yield, respectively). A plausible biosynthetic relationship between acyclic tatanan A and spirocyclic tatanans B and C is proposed and probed experimentally. With sufficient quantities of the natural products in hand, we undertake a detailed functional characterization of the biological activities of tatanans A–C. Contrary to previous reports, our assays utilizing pure recombinant human enzyme demonstrate that tatanans do not function as allosteric activators of glucokinase.

Small-molecule allosteric activators of human glucokinase have generated considerable interest as potential therapeutic agents for the treatment of type 2 diabetes¹. These molecules are effective at stimulating insulin secretion from pancreatic β -cells and thereby rapidly reducing plasma glucose levels in animal models². At least one glucokinase activator, piragliatin, has advanced to phase II clinical trials in humans³. The first glucokinase activator was described in 2003⁴, and since that time pharmaceutical chemists have identified a variety of unique chemical scaffolds capable of stimulating glucokinase activity *in vivo*⁵. Although all glucokinase activators investigated to date are synthetic, the recent discovery of the tatanans, a novel class of naturally occurring lignan derivatives that reportedly possess potent glucokinase-activating capabilities, suggests that natural products might represent a rich resource for structurally and mechanistically new antidiabetic agents^{6,7}. As a first step in exploring tatanans and the derivatives thereof as potential diabetes therapeutics, we undertook the total chemical synthesis and detailed mechanistic characterization of the glucokinase-activating properties of tatanans A, B and C.

Lignans are a large class of polyphenolic natural products related to oligostilbenes^{8,9} but distinct in their basic monomeric unit¹⁰. Tatanans are structurally unique sesquilignans recently isolated from the ethyl acetate extracts of rhizomes of *Acorus tatarinowii* Schott plants⁶. Tatanan A incorporates three consecutive tertiary stereocentres and three aryl substituents appended to an acyclic framework. Tatanans B and C, on the other hand, are cyclic atropisomers characterized by complex spirocyclic architectures that combine a cyclohexane ring substituted at each position with a 2,5-cyclohexadienone subunit. The existence of atropisomerism in tatanans B and C is evidently a consequence of the restricted rotation around the C1–C7 bond that links ring A, proximal to the quaternary stereogenic centre at the spirocyclic ring junction,

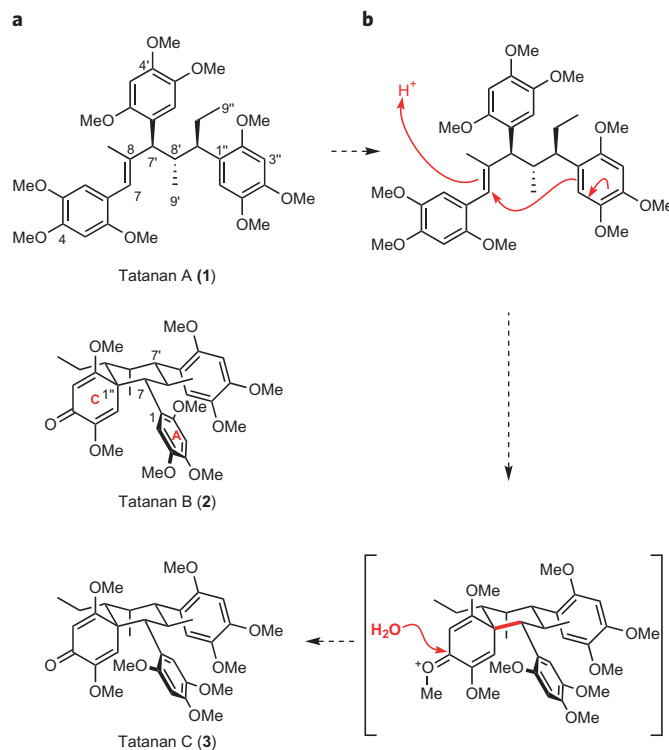


Figure 1 | Tatanans A–C are structurally unusual novel sesquilignans isolated from the rhizomes of *Acorus tatarinowii* plants. These natural products have been reported to potently activate glucokinase. **a**, Structure of tatanans. **b**, Proposed biosynthetic relationship between acyclic tatanan A and spirocyclic tatanans B and C.

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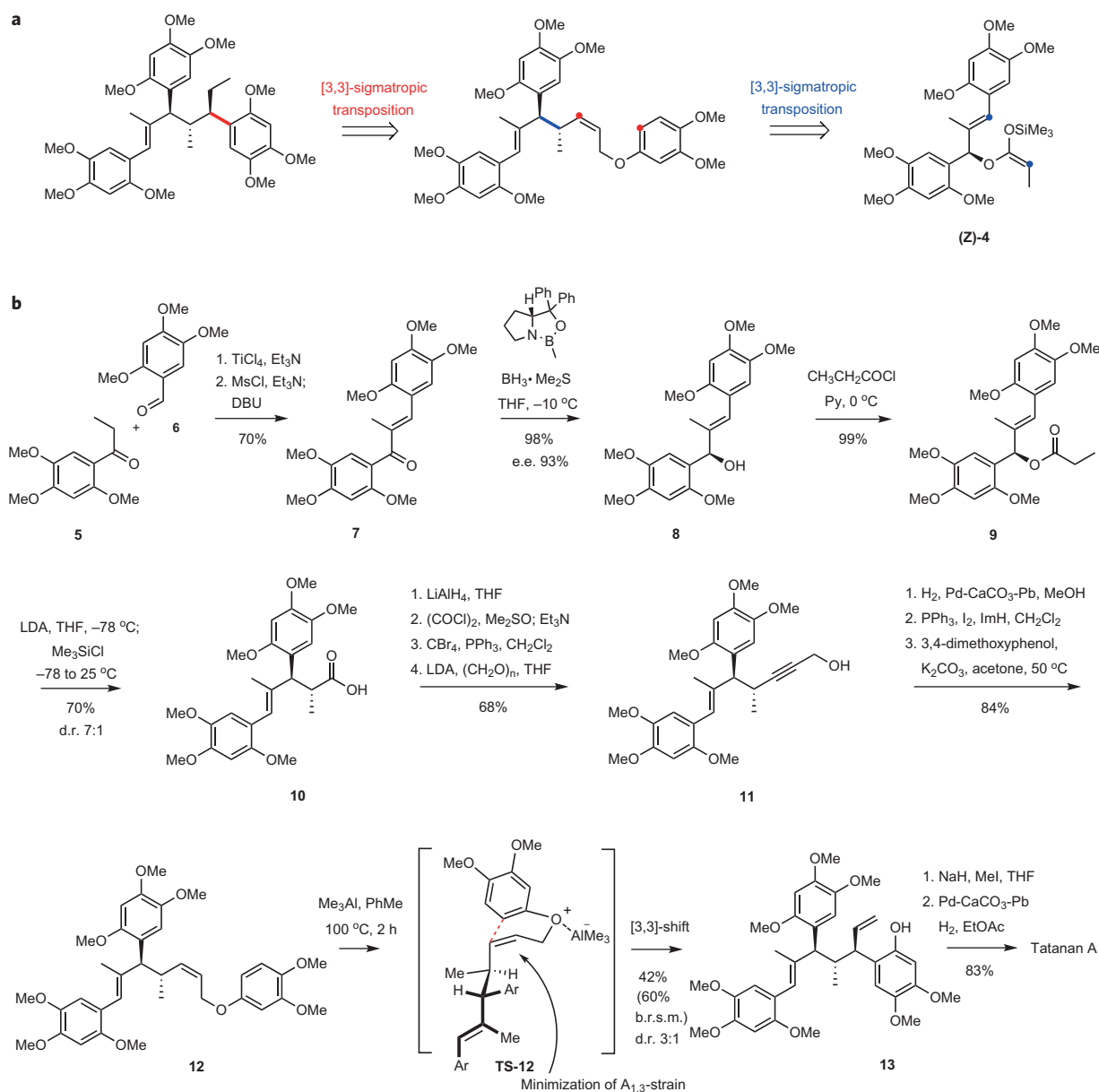


Figure 2 | Description of the total synthesis of tatanan A using consecutive sigmatropic rearrangements as a key element of the synthesis design, setting the three adjacent stereogenic centres of the natural product. **a**, Outline of the synthesis plan for tatanan A, illustrating the application of the [3,3]-sigmatropic transforms. **b**, Full reaction sequence for the enantioselective synthesis of tatanan A, 15 steps from aldehyde **6** and ketone **5**. Ms, methanesulfonyl; DBU, 1,8-diazabicycloundec-7-ene; THF, tetrahydrofuran; Py, pyridine; LDA, lithium diisopropylamide; ImH, imidazole.

to the cyclohexane subunit. This type of molecular structure is unprecedented among known lignans^{11,12}, enhancing our interest in developing a concise chemical synthesis of these natural products. We postulated that acyclic tatanan A is biosynthetically interrelated to its spirocyclic congeners through a stereospecific electrophilic ring-closing dearomatization initiated by a proton donor, as illustrated in Fig. 1b¹³. Thus, an additional goal of our synthesis efforts was to investigate the facility of such a transformation.

Results and discussion

Total synthesis of tatanans A–C. Tatanan A, with its three consecutive all-carbon tertiary stereogenic centres, became the initial goal of our synthesis efforts. Iterative application of [3,3]-sigmatropic rearrangements formed the basis of the synthesis design (Fig. 2a)¹⁴, and its concise implementation is presented in Fig. 1b. Aldol condensation of ethyl 2,4,5-trimethoxyphenyl

ketone (**5**) with 2,4,5-trimethoxybenzaldehyde promoted by titanium tetrachloride provided ketone **7** in 70% yield¹⁵. Enantioselective reduction of this to allylic alcohol **8** was accomplished using (*R*)-2-methyl-CBS-oxazaborolidine (CBS = Corey-Bakshi-Shibata; 98% yield, 93% e.e.)¹⁶. The formation of the propargylic ester of **8** in nearly quantitative yield was followed by the Ireland-Claisen rearrangement¹⁷, which proceeds through an initial *Z*-selective enolization with lithium diisopropylamide, trapping of the lithium enolate with chlorotrimethylsilane to give the ketene acetal (*Z*)-**4**, and its relatively rapid rearrangement via a chair-like transition structure at 25 °C over the course of 1 h. This key constructive transformation^{18,19} establishes the requisite configuration at the C7' and C8' stereocentres with good stereocontrol (d.r. 7:1, 70% yield). Propargylic alcohol **11** was accessed in four steps that included a reduction-oxidation sequence to reduce the carboxy group in **10** to the aldehyde,

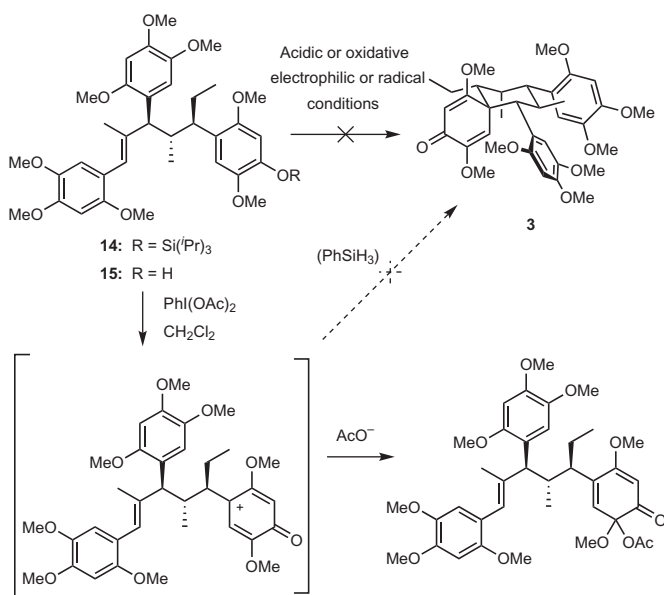


Figure 3 | Tatanans B and C can conceivably arise from cyclization of tatanan A during their biosynthesis. The total synthesis of tatanan A enabled an exploration of biomimetic cyclization of tatanan A derivatives to tatanans B and C, which proved unsuccessful under a variety of cationic or radical reaction conditions.

conversion of the aldehyde to the 1,1-dibromoalkene upon treatment with carbon tetrabromide and triphenylphosphine, and formation of the lithium acetylenide followed by quenching with paraformaldehyde, affording **11** in 68% overall yield. Selective hydrogenation with Lindlar's catalyst and two-step aryl ether formation provided **12** in 84% overall yield.

Lewis-acid mediated [3,3]-sigmatropic rearrangement²⁰ of (*Z*)-allylic aryl ether **12** secured the stereochemistry of the remaining chiral centre while completing the carbon framework of tatanan A. Phenol **13**, isolated in 42% isolated yield (60% based on recovered starting material, b.r.s.m.), was formed in a diastereoselective process that favoured the desired stereoisomer with a 3:1 selectivity. The *Z* configuration of the double bond was necessary to enhance diastereocontrol. The major stereoisomer presumably arises through a reaction pathway involving transition structure **TS-12**, which is favoured due to minimization of allylic strain. Rearrangement of the corresponding (*E*)-allylic ether provided an approximately 1:1 mixture of stereoisomers. Starting from rearrangement product **13**, the completion of enantioselective synthesis of tatanan A required only two additional steps. Methylation of the phenolic hydroxyl (NaH, CH₃I, THF) followed by chemoselective hydrogenation of the terminal alkene in the presence of Lindlar's catalyst delivered 26 mg of tatanan A (83% yield over two steps). Synthetic tatanan A showed identical spectroscopic data (¹H and ¹³C NMR) to those published for the natural product; the optical rotation for the synthetic material was of the same sign but of a notably higher value ($[\alpha]_D^{20} + 55$ (*c* 0.1, CH₃OH); literature⁶ $[\alpha]_D^{20} + 10$ (*c* 0.1, CH₃OH)).

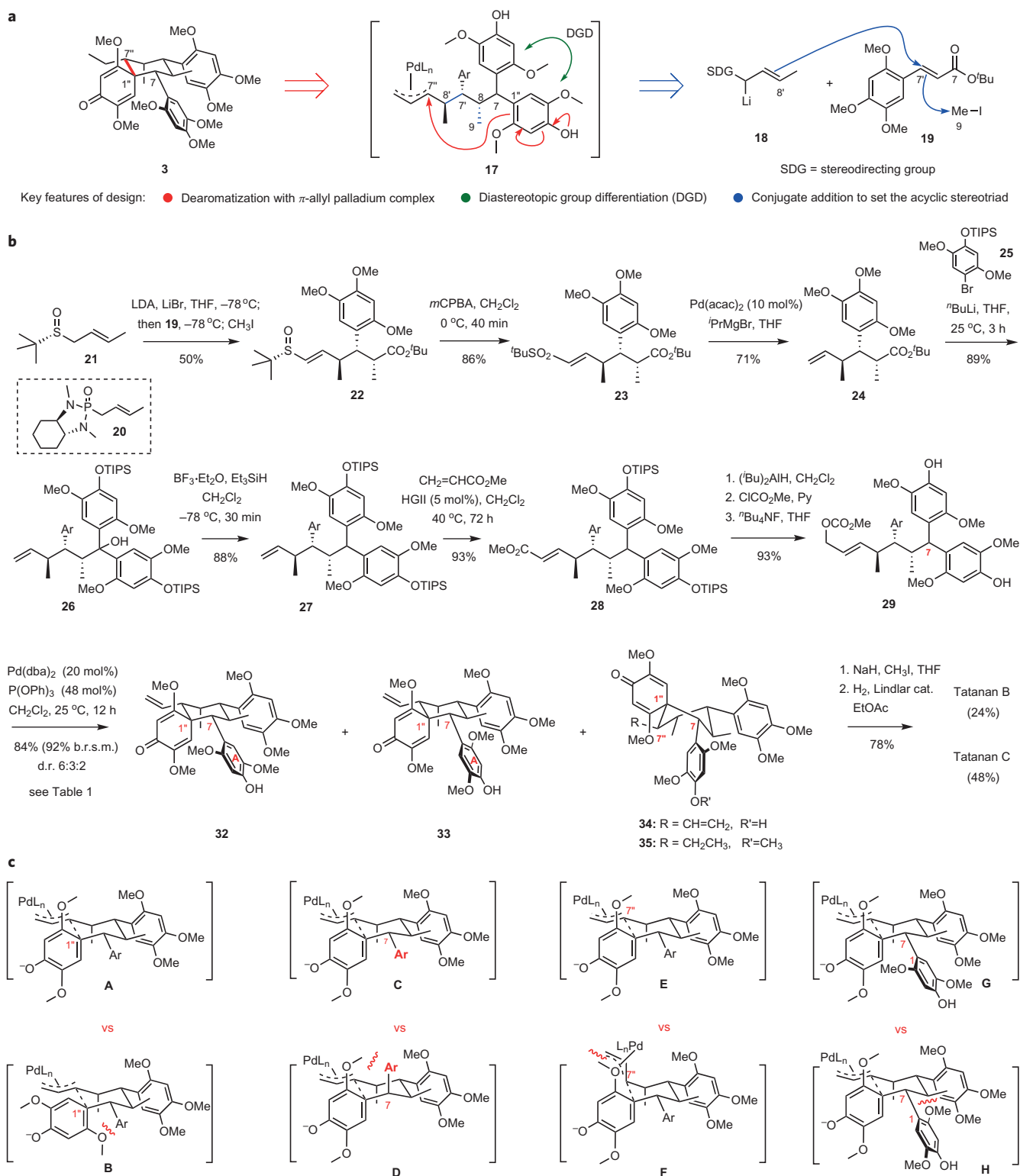
The synthesis of tatanan A on the aforementioned scale enabled a study exploring its conversion to spirocyclic tatanans B and C, emulating the proposed biosynthetic pathway depicted in Fig. 1b^{21,22}. The C4'' triisopropylsilyl ether **15** was prepared via straightforward modification of reactions used in the total synthesis of tatanan A (Fig. 3). Exposing the C4'' phenolic hydroxyl was expected to activate ring C as a nucleophilic counterpart in the cyclization. Under a variety of acidic reaction conditions, **15** failed to undergo cyclization to tatanans B or C. For example, treatment

with 2.5 mM CF₃SO₃H/CH₂Cl₂ at 0–25 °C resulted initially in no reaction, and then decomposition to an intractable mixture of products at higher temperature. No reaction was observed under milder conditions with pyridinium tosylate in CH₂Cl₂ or aqueous CH₃OH. Next, an approach was explored based on reversed polarity in the cyclization, which again met with no success. Electrophilic or radical activation of ring C in **15** by oxidation with hypervalent iodine reagents (PhI(OAc)₂, PhI(O₂CCF₃)₂) in the presence of a hydride donor (PhSiH₃) only resulted in the formation of benzoquinone products, and no spirocyclization to tatanans B or C was observed. These observations suggest that the postulated biosynthetic assembly of tatanans B and C by cyclization of tatanan A is unlikely to occur without the assistance of an enzyme.

Accomplishing the synthesis of the structurally complex tatanans B and C required a reformulated approach. The key recourse in developing a new synthesis plan was to reposition the ring-opening bond scission from C7–C1'' to C1''–C7'' (Fig. 4a). To enable this strategy, a phenol dearomatization through intramolecular allylation by a π -allyl palladium complex was envisioned, which was expected to occur with diastereotopic group differentiation and set three consecutive stereogenic centres of the fully substituted cyclohexane ring in one step. A precursor of acyclic intermediate **17** was to be assembled in a convergent manner by asymmetric conjugate addition of an (*E*)-crotyllithium reagent **18**, where SDG is a stereodirecting group, to cinnamic ester **19**. Alkylation of the ester enolate arising from the conjugate addition with methyl iodide was expected to build the stereotriad found in **17** in an expedient manner.

Implementation of the amended synthesis plan was initiated via the development of a suitable conjugate addition method (Fig. 4b). Addition of the lithiated crotyl phosphoramidate to ester **19** with subsequent alkylation of the intermediate enolate with iodomethane, following the protocol developed by Hanessian and co-workers²³, delivered the expected product in high yield and with outstanding diastereocontrol. However, various attempts to remove the vinylic phosphoramidate substituent proved to be prohibitively inefficient, prompting us to seek a more practical alternative. Addition of the lithiated (*R*)-*tert*-butyl (*E*)-2-butenyl sulfoxide²⁴ **21** occurred with high diastereoselectivity, delivering ester **22** as a single diastereomer in 50% yield after *in situ* methylation of the transient ester enolate²⁵. Diastereoisomeric products resulting from α -alkylation of the sulfoxide accounted for the remainder of the mass balance. Oxidation of the sulfoxide to sulfone followed by a palladium-catalysed desulfonation (Pd(acac)₂, *i*-PrMgBr) afforded terminal alkene **24** in good yield²⁶. The diastereotopic aryl groups were introduced at this stage by addition of 2 equiv. of the aryllithium reagent derived from **25** through lithium–bromine exchange, followed by electrophilic reduction of **26** with Et₃SiH in the presence of BF₃–etherate²⁷. The cross-metathesis reaction²⁸ between **27** and methyl acrylate using the Hoveyda–Grubbs II catalyst effectively provided α,β -unsaturated ester **28**, which was converted to allyl methyl carbonate in three steps and 86% overall yield.

For the critical assembly of the spirocyclic ring system, a transition metal-catalysed cyclization with concomitant dearomatization and diastereotopic aryl group differentiation was selected as the preferred tactical solution (Fig. 4a)²⁹. Although intramolecular metal-catalysed allylic dearomatization is a powerful approach to the synthesis of spirocyclic cyclohexanediones, to date there are no applications of this methodology in the total synthesis of complex natural products³⁰. Very recently, two reports describing methodological studies on direct intramolecular C-allylation of phenols have appeared in the literature, demonstrating the feasibility of this process. In 2010, Hamada and co-workers³¹ described a palladium-catalysed spirocyclization forming a spiro[4.5]decane ring system. In that study, a single example was reported that afforded a spirocyclic ring system containing two six-membered



rings. In 2011, You and colleagues reported a related iridium-catalysed dearomatization producing a 3-azaspiro[5.5]undecadienone, together with numerous examples of intramolecular allylation giving spiro[4.5]decane ring systems³².

In the context of this total synthesis endeavour, intramolecular allylic dearomatization of complex substrate **29** was investigated concentrating on palladium(0) and iridium(i) catalysis (Table 1). We found that iridium-catalysed reactions were ineffective (entries 1 and 2)³². In contrast to Hamada's findings, the rate of allylic dearomatization of **29** under palladium catalysis is substantially enhanced with decreasing σ -donor capacity of the phosphine ligand (entries 3–7). Although little to no conversion has been observed with PPh₃ or P(*o*-tol)₃, the reaction took place with complete conversion in the presence of P(2-furyl)₃, P(OPh)₃ or P(OEt)₃. Using palladium(II) acetate and triphenylphosphine as the source of the catalyst resulted in the formation of only a trace amount of the expected product (entry 9). Interestingly, a somewhat slower rate was observed when Pd₂(dba)₃ was used in place of Pd(dba)₂ as the source of the active catalyst (entry 10).

Under optimized conditions, the desired cyclization could be achieved cleanly upon treatment with Pd(dba)₂ and P(OPh)₃, affording an inseparable mixture of atropisomeric products **32** and **33** together with C1'',C7''-diastereomer **34** in 84% combined yield (92% based on recovered starting material, d.r. 6:3:2, respectively). During this operation, three of the six stereocentres of the target molecule, including the quaternary centre at the core of the spirocyclic ring system, are set with a high degree of stereocontrol. Only three of 16 possible stereoisomers have been observed.

The stereochemical course of the spirocyclization reaction can be understood by considering chair-like transition structures A–H (Fig. 4c), where the non-reacting aryl group resides in the equatorial position, and minimization of steric interactions between the *ortho*-methoxy substituents delivers the observed products. Each of the four pairs of transition structures demonstrates preferences within the four corresponding stereochemical categories operative in the palladium-catalysed cyclization, namely (i) selectivity in the formation of the quaternary centre at C1'' (A versus B); (ii) diastereoselectivity at C7 (C versus D); (iii) selectivity at the vinyl-substituted centre C7'' (E versus F); and (iv) atropselectivity around the C1–C7 bond (G versus H). Although stereocontrol for the formation of the quaternary centre is high, control over the axial selectivity around the C1–C7 bond only reached a moderate level of ~3:1. In minor isomer **33**, the 2-MeO group of ring A is situated in the sterically hindered position, eclipsing the cyclohexane subunit. Nevertheless, the formation of atropisomers **32** and **33** enabled eventual access to both natural products: tatanan B and tatanan C. A minor amount of **34** is also formed, probably by a competing pathway proceeding through a boat-like transition structure.

The synthesis of tatanans B and C was readily accomplished in two direct steps from **33** and **32**, respectively: (i) phenol methylation and (ii) chemoselective hydrogenation of the vinyl group (H₂, Lindlar's catalyst, EtOAc; 78% yield over two steps). The atropisomeric tatanans B and C were separated by preparative reverse-phase HPLC. Completion of the total chemical synthesis delivered 30 mg of (–)-tatanan C and 15 mg of (–)-tatanan B. The synthetic material was spectroscopically identical to the natural products (¹H and ¹³C NMR in two different solvents: CD₃OD and (CD₃)₂CO); however, the data for the absolute optical rotation were substantially different (tatanan B: [α]_D²⁰ –30 (c 0.10, CH₃OH); literature⁶ [α]_D²⁰ 0 (c 0.1, CH₃OH); tatanan C: [α]_D²⁰ –47 (c 0.11, CH₃OH); literature⁶ [α]_D²⁰ 0 (c 0.1, CH₃OH)).

Biological studies. Following the initial discovery and structural characterization of tatanans by Yu and co-workers, bioactivity studies suggested that these novel natural products display antidiabetic activity through an ability to allosterically activate human pancreatic glucokinase⁶. This finding was intriguing, as tatanans appear to represent the first example of a biogenic glucokinase activator. Moreover, the reported bioactivities of tatanans A–C exceed that of a known, potent synthetic activator, derivatives of which are currently under investigation as therapeutic agents³. However, initial characterization of the glucokinase-activating properties of tatanans was limited, presumably due to the small quantities of tatanan A, B and C isolated from natural sources. Our successful total synthesis efforts provided substantial quantities of all three compounds, thus enabling a detailed mechanistic investigation of the glucokinase-activating characteristics of the tatanans. Previous work indicated that tatanan C was the most potent congener, with an EC_{1.5} value (concentration of compound required to increase enzyme activity by 50%) of 0.16 μ M toward human glucokinase⁶. Based on this finding, our initial biochemical characterization efforts focused on tatanan C.

Recombinant human pancreatic β -cell glucokinase was produced and purified to greater than 95% purity using established procedures³³, and the enzyme was used in assays to evaluate the impact of tatanan C upon the kinetic parameters of glucokinase. As a control, we also characterized the activation properties of RO-28-1675, a previously described synthetic glucokinase activator that has served as a lead compound for therapeutic development⁴. Consistent with previous reports, RO-28-1675 is a potent glucokinase activator that elicits a tenfold decrease in the glucose K_{0.5} value and a 30% increase in the k_{cat} value (Fig. 5). Similar to other synthetic activators, RO-28-1675 also produces a reduction in the kinetic cooperativity of human glucokinase, as reflected by a lower Hill number. In contrast to RO-28-1675, the presence of

Table 1 | Optimization studies for the key intramolecular allylic spiro-dearomatization.

Entry	Catalyst	Ligand	T (°C)	Time (h)	Yield of 32 + 33 (%)	32:33
1	[Ir(COD)Cl] ₂	P(OPh) ₃	25	36	0	
2*	[Ir(COD)Cl] ₂	P(OPh) ₃	25	36	10	1:1
3	Pd(dba) ₂	PPh ₃	25	36	30	3.5:1
4	Pd(dba) ₂	P(<i>o</i> -tol) ₃	25	36	0	
5	Pd(dba) ₂	P(2-furyl) ₃	25	12	69	2.5:1
6	Pd(dba) ₂	P(OEt) ₃	25	12	75	2.5:1
7	Pd(dba) ₂	P(OPh) ₃	25	24	76	1.9:1
8 [†]	Pd(dba) ₂	P(OPh) ₃	25	12	84 (92% b.r.s.m.)	2.0:1
9 [‡]	Pd(OAc) ₂	PPh ₃	50	24	<1	
10	Pd ₂ (dba) ₃	P(OPh) ₃	25	24	51 (76% b.r.s.m.)	1.4:1

Typical reaction conditions: substrate (15 mg) was stirred with catalyst (20 mol%) and ligand (48 mol%) in CH₂Cl₂ under argon.

*Cs₂CO₃ (2 equiv.) was used as an additive.

[†]Performed on 100 mg scale.

[‡]Ti(OPr-*i*)₄ (2 equiv.) was used as an additive.

COD, 1,5-cyclooctadiene; dba, dibenzylideneacetone; b.r.s.m., based on recovered starting material.

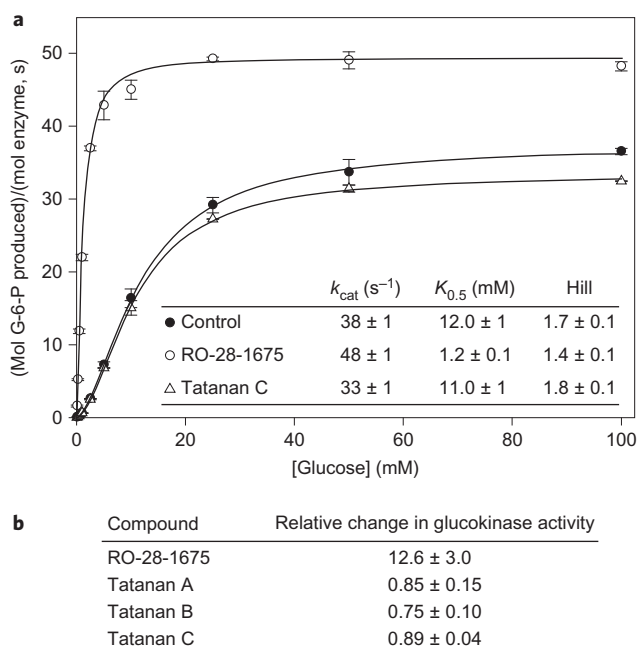


Figure 5 | In vitro enzymatic assays demonstrate that tatanans A-C do not activate human glucokinase. **a**, Glucokinase activation assays conducted in the absence (control) and presence (20 μ M) of tatanan C and a previously described synthetic activator, RO-28-1675 (20 μ M). RO-28-1675 activates glucokinase by increasing the k_{cat} value, decreasing the glucose $K_{0.5}$ value, and reducing the Hill coefficient. Tatanan C has no effect on these catalytic constants. Experimental rate data for each glucose concentration represent the average of two or more independent assays, with the standard deviation of the mean represented by the vertical bars. Kinetic constants were obtained from the fit of the experimental data to the Hill equation and represent the average of two or more complete kinetic profiles. G-6-P, glucose-6-phosphate. **b**, RO-28-1675 produces a 12.6-fold increase in relative glucokinase activity, while tatanans A, B and C do not increase enzyme activity. Activity changes were calculated from the ratio of enzymatic second-order rate constants ($[k_{cat}/K_{0.5} \text{ activated}]/[k_{cat}/K_{0.5} \text{ control}]$) determined in the presence and absence of 20 μ M activator.

tatanan C at concentrations up to 20 μ M failed to produce measurable changes in the kinetic profile and properties of human glucokinase (Fig. 5). Higher concentrations of tatanan C were not explored due to the limited solubility of this compound under aqueous conditions; however, the concentrations used in our study are more than an order of magnitude higher than the $EC_{1.5}$ values reported in the initial description of the tatanans.

We next investigated the bioactivities of the two remaining sesquignans, tatanan A and B. Although the reported activities for tatanan A and B towards glucokinase are somewhat lower than that of tatanan C, both compounds displayed $EC_{1.5}$ values (1.85 and 0.52 μ M, respectively⁶) that are readily accessible with enzyme activity assays. Similar to the tatanan C results, the inclusion of tatanan A and B at concentrations up to 20 μ M did not produce an increase in glucokinase activity over control reactions (Fig. 5b). In contrast, the known activator RO-28-1675 produced a 12.6-fold increase in the second-order rate constant for enzyme catalysis, $k_{cat}/K_{0.5}$.

Conclusions

The concise, step-economical^{34,35} synthesis of novel sesquignans tatanans B and C was accomplished by an intramolecular palladium-catalysed allylic phenol dearomatization of a complex substrate. This transformation includes a diastereotopic aryl group differentiation and effectively sets three of the six stereocentres of

the densely substituted cyclohexane unit present in these molecules. The atropisomeric products are formed in \sim 2:1 ratio and converted to atropisomeric tatanans B and C, completing the total synthesis in 13 steps from 2,4,5-trimethoxybenzaldehyde. Tatanan A was prepared concisely by a strategy based on consecutive [3,3]-sigmatropic rearrangements, allowing us to experimentally probe its putative biosynthetic relation to spirocyclic tatanans B and C.

The observation that tatanans exhibit no glucokinase activation under all conditions investigated herein strongly supports the conclusion that tatanans are not antidiabetic, allosteric activators of glucokinase. The reason for the discrepancy between our bioactivity assays and previous reports⁶ is unclear, as both investigations utilized the same enzymatic assay for glucokinase activity. Notably, Ni and co-workers measured glucokinase activity at only a single glucose concentration⁶, whereas we determined the full kinetic profile of glucokinase in the presence and absence of potential activators. In addition, the assay conditions used by Ni and co-workers involved a non-optimal ratio of reagents; however, we also conducted assays under these non-ideal conditions and failed to observe glucokinase activation. The possibility that another natural product of unknown structure co-purified with tatanans during the initial isolation of these compounds, and is responsible for the previously observed activation of glucokinase, remains to be investigated. Our successful development of a concise and high-yielding synthetic strategy for tatanans, and derivatives thereof, will enable a broad investigation of the biological activities of these structurally unique natural products.

Received 22 August 2012; accepted 7 February 2013;
published online 24 March 2013; corrected online 4 April 2013

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Acknowledgements

The authors thank Hongjun Zhou for continued assistance with NMR spectroscopy. This work was supported by the US National Institutes of Health (NIGMS GM077379 to A.Z., NIDDK DK081358 to B.G.M.) and additional kind donations from Eli Lilly and Amgen.

Author contributions

Q.X., A.B., J.J.J. and J.M.B. planned, conducted and analysed the experiments. A.Z. and B.G.M. designed and directed the project. A.Z. and B.G.M. wrote the manuscript. All authors contributed to discussions.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to B.G.M. (bioassays) and A.Z. (chemical synthesis).

Competing financial interests

The authors declare no competing financial interests.