An expeditious one-step entry to the tetracyclic core of integrastatins†

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Herein we describe a one-step assembly of structurally complex small molecules representing the central skeleton of integrastatins by employing a simple pinacol transform.

Demand for the construction of architecturally complex molecules from simple building blocks has attained special importance in the realm of diversity oriented synthesis.[1] Accessing distinctive three-dimensional architectures by employing structurally simplifying transforms from easily available starting compounds, remains as a challenging problem, especially when the targets are required in a fewer steps.[2] Domino reactions characterized by several bond formations through sequential intramolecular transformations are well outfitted to address the above issues.[3] We report such a domino process comprising a low-valent titanium mediated pinacol cross coupling[4] and an intramolecular trapping of the resulting vicinol diol with a suitably disposed carbonyl group. This process results in a one-step assembly of the central core of integrastatins.

Integrastatin A (**1**) and B (**2**) (Fig. 1), which are potent HIV integrase inhibitors, were isolated from two different fungal sources [an unidentified fungal source (ATCC74478) and from an endophytic *Ascochyta* species (ATCC74477)] by Singh *et al.* in 2002 as the first examples of a novel tetracyclic aromatic [6/6/6/6/]-heterocycle.[5] The unique structural features and important biological activity of these molecules confer them as attractive targets of synthetic chemists. However, to date, there is only a single preliminary report by Taylor and co-workers for the synthesis of the integrastatin central core, which utilizes the Ramberg–Backlund reaction and an unusual Lewis acid-promoted cyclization.[6] Considering the importance of integrase as an emerging therapeutic target in anti-retroviral drug development programs,[7] a flexible approach in this context will bestow a significant incentive for structure–activity studies. As shown in Fig. 1, disconnection of the central core of integrastatin B between C(9)–C(10) after oxidation state adjustment at C(9) revealed a striking feature that **2** is a pinacol cross-dimer of a *o*-ketoaldehyde **3**.

Inspired by the simplicity of the retrosynthetic strategy, the feasibility of projected transformation was examined by employing commercially available *o*-phthalaldehyde (**4**) and *o*-hydroxybenzaldehyde (**5**) employing some of the available

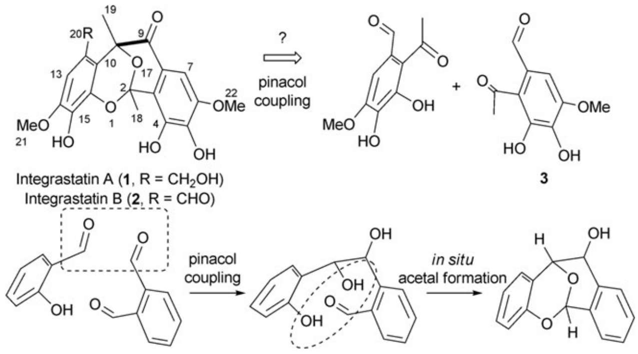
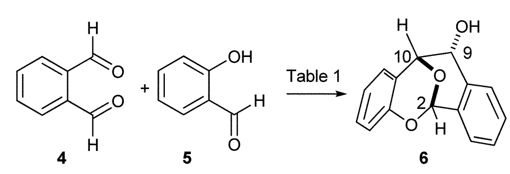


Fig. 1 Integrastatins A (**1**) and B (**2**) and identified pinacol transform for the central tetracyclic aromatic 6/6/6/6/-heterocyclic core.

pinacol conditions.[8–12] As indicated in Scheme 1, the proposed transformation was found to be feasible with the low-valent titanium reagent generated *in situ* by employing Zn–Cu,[8] Zn,[9] or, best of all, Mg(Hg).[10] The reaction in general results in a complex mixture and the products were isolated and identified by flash chromatography and NMR spectroscopy, respectively.[13]

The assigned *threo*-configuration for compound **6** was derived from the NMR spectral studies.[14] For example, in the ^{1}H NMR spectrum of **6**, the bicyclic acetal H-2 (δ 6.30 ppm, s) appeared downfield compared to the other two benzylic protons H-9 (δ 5.27 ppm) and H-10 (δ 5.14 ppm). H-10 resonated as a sharp doublet with J = 5.9 Hz characteristic of axial–equatorial coupling. Energy minimization calculations for both the possible diastereomers revealed a



Reagents and conditions:

S. No.	Conditions[8-12]	Yield
1	[8]15% aq.solution of $TiCl_3$, acetone, r.t.	7%
2	[9]Zn, $TiCl_4$, THF, 0 °C	21%
3	[10]Mg(Hg), $TiCl_4$, THF, 0 °C	42%
4	[11]cat. Cp_2TiCl_2, Zn, TMSCl, THF, r.t.	15%
5	[12]Mg, TMSCl, Cat $InCl_3$, THF, r.t.	No reaction

Scheme 1 Pinacol coupling of *o*-phthalaldehyde and *o*-hydroxybenzaldehyde.

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† Electronic supplementary information (ESI) available: Details of X-ray structural analyses of compounds **6** and **16**, spectral data for all new compounds. CCDC 676602 and 676603. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b801755g

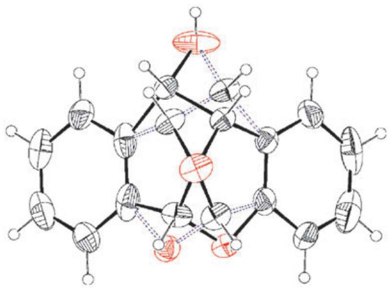


Fig. 2 The molecular structure of the tetracyclic compound **6**. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of an arbitrary radius.

preference for the half-chair conformation for rings B and C, and an axial disposition for the β-functional group at C(10). Finally, single-crystal X-ray analysis (see CCDC 676602, ESI†) of compound **6** (Fig. 2) confirmed the proposed relative configuration.

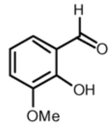
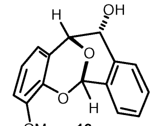
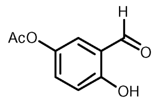
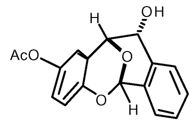
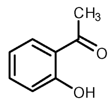
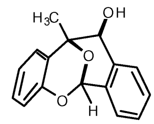
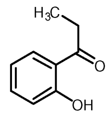
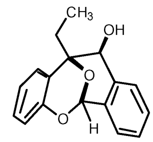
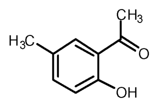
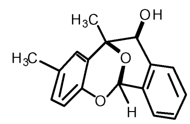
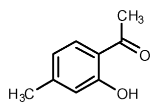
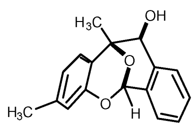
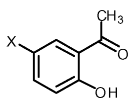
All attempts (solvent/temperature, mol ratio variations) to optimize yields for entry 3 (Scheme 1) were not encouraging and hence the same conditions [Mg(Hg), $TiCl_4$, THF, 0 °C] were used for the generalization of this reaction with other commercially available *o*-hydroxybenzaldehydes **7–8**, and with *o*-hydroxy acetophenones **9–15** (Table 1). The relative configuration of products **16** and **17** obtained from the reactions of aldehydes **7** and **8**, respectively, was assigned as *threo* by comparing their chemical shifts and coupling constants with that of **6**. The single-crystal X-ray structural analysis of **16** (see CCDC 676603, ESI†) (Fig. 3) further confirmed the assigned structure.

With arylketones **9–12** (Table 1) the corresponding tetracyclic derivatives **18–21** were obtained in moderate yields. We could not isolate any expected products from the cross pinacol coupling reaction of **4** with halogen substituted acetophenones (**13–15**, entry 7). The stereochemistry of the tetracyclic compound **18** was established as *erythro* with the help of NOESY studies. For example, a strong nOe observed between the methyl group and the benzylic-H clearly indicated a close spatial proximity between these groups (Fig. 4). The benzylic-H displayed spatial interaction with *ortho*-hydrogens of both the aromatic rings revealing a *syn*-periplanar arrangement. MM2 calculations revealed that such a close proximity is possible when the benzylic-H is *syn* to the adjacent methyl group.

After generalization of the projected one-step assembly using *o*-phthalaldehyde, we next attempted the coupling reaction of 2-formylacetophenone[15] with **9** in order to bring in the methyl group corresponding to C18 of the integrastatin core. Although, the majority of the products could be separated and checked for their constitution, none of them were found to match with the expected product. Subsequently, to show the feasibility of projected benzylic-OH oxidation, one of the intermediates **18** was treated with MnO_2 (Scheme 2) and the corresponding keto compound **22** was obtained in good yield.

In summary, a facile one-step approach for the central tetracyclic core of integrastatins by employing low-valent titanium mediated pinacol cross coupling reaction has been documented. The present approach is characterized by consecutive formation of three bonds affording topologically complex tetracyclic compounds. This adds another facet to the pinacol reaction with a potential to be extended for other structurally complex molecules by judicious substrate design. Work in this direction is progressing in our laboratory.

Table 1 Pinacol coupling of **4** with *o*-hydroxybenzaldeldehydes and acetophenones under optimized conditions

Entry	Substrate	Product	Yield (%)
1	 **7**	 **16**	47
2	 **8**	 **17**	57
3	 **9**	 **18**	49
4	 **10**	 **19**	37
5	 **11**	 **20**	43
6	 **12**	 **21**	41
7	 **13 – 15** X = F, Cl, Br	—	—

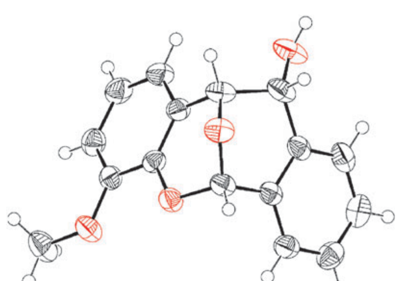


Fig. 3 The molecular structure of the tetracyclic compound **16**. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of an arbitrary radius.

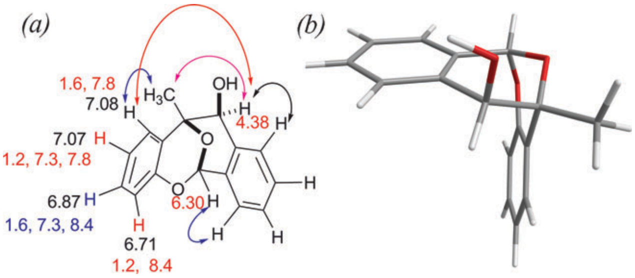
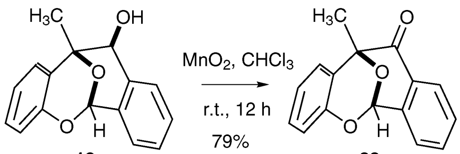


Fig. 4 (a) Observed through-space interactions and (b) MM2 energy minimized structure for the erythro isomer revealing relative orientation of two aromatic protons and the benzylic-H.



18 22

Scheme 2 Benzylic oxidation of compound **18**.

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13. *General procedure for pinacol cross-coupling reactions*: At −10 °C, a suspension of Mg(Hg) [prepared from $HgCl_2$ (200 mg, 0.74 mmol) and Mg (720 mg, 30 mmol) according to Corey's procedure[10a]] in THF (5 ml) was treated dropwise with $TiCl_4$ (2.82 g, 14.9 mmol) followed by a solution of **4** (510 mg, 3.7 mmol) and **5** (450 mg, 3.72 mmol) in THF (10 ml). The resulting purple mixture was stirred for 1.5 h at 0 °C, treated with aq. K_2CO_3 solution (1.5 ml), and stirred at 0 °C for 15 min. Diethyl ether (10 ml) was added and the mixture was filtered through Celite. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated. The crude product was subjected to flash column chromatography to afford **6** (370 mg, 42%).
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