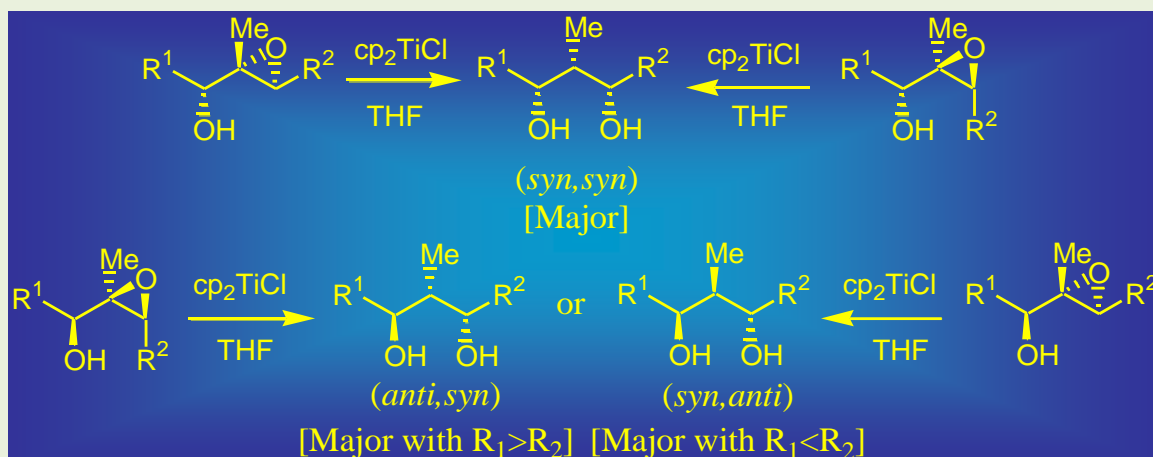


Synthesis of natural products and strategies to develop analogous molecules

Some recent works

Ti(III)-Mediated Stereoselective Radical Reactions: Application in the Synthesis of Natural Products

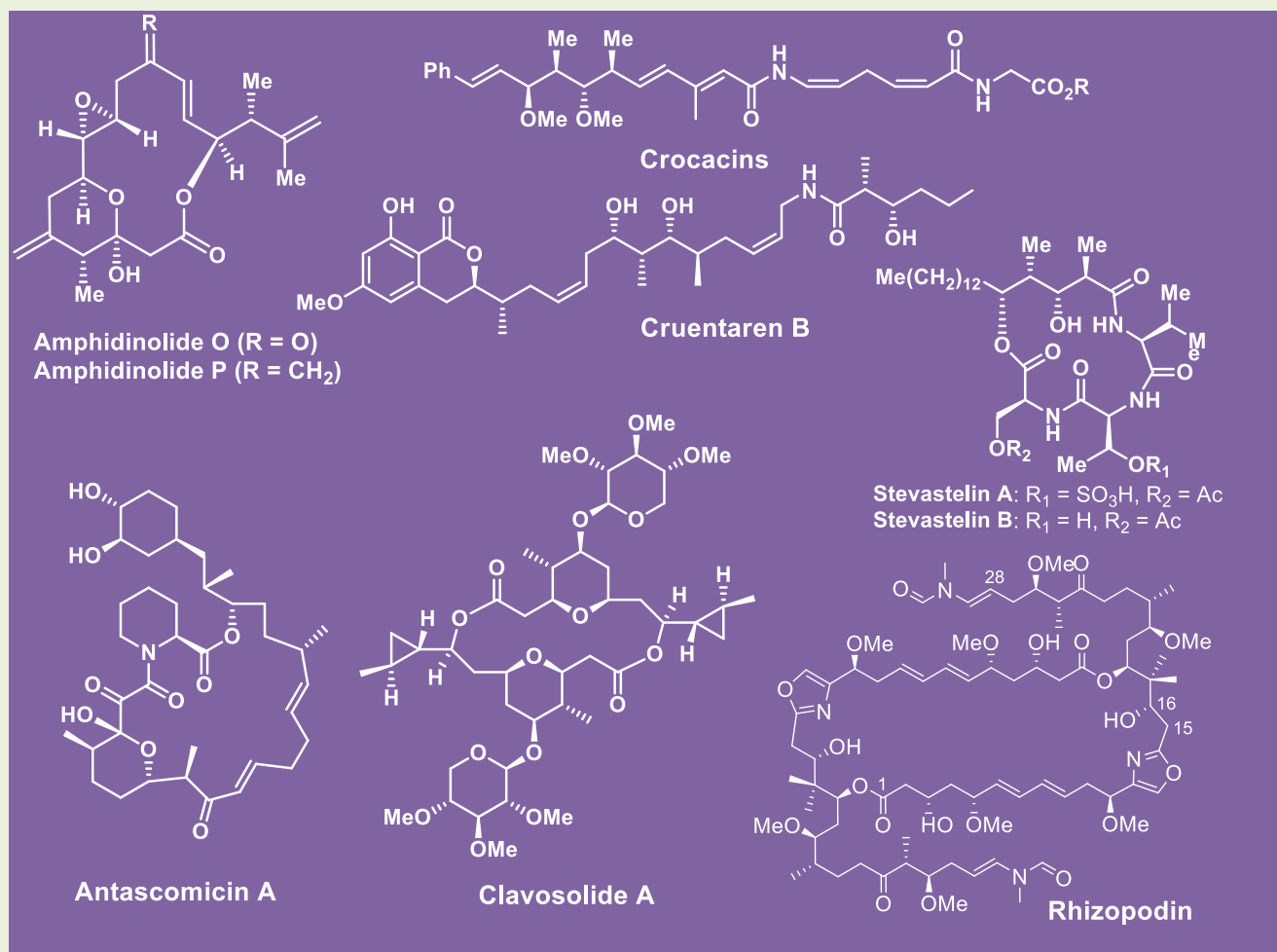


References: (a) "Anti-Markovnikov Opening of trisubstituted Epoxy Alcohols: Application in the synthesis of 2-Methyl-1,3-Diols" Tushar Kanti Chakraborty and Shantanu Dutta *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257–1259. (b) "Synthesis of chiral 1,3-diols by radical-mediated regio-selective opening of 2,3-epoxy alcohols using cp_2TiCl " Tushar Kanti Chakraborty and Sanjib Das *Tetrahedron Lett.* **2002**, 43, 2313–2315.

An efficient method for stereoselective synthesis of 1,3-diols, especially with 2-substitution, was developed in our lab using Ti(III)-mediated radical ring opening of various substituted 2,3-epoxy alcohols. The general strategy is depicted above.

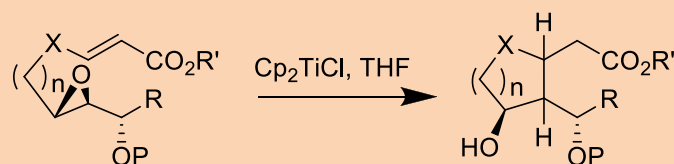
The above method has been successfully applied by us in the synthesis of many polyketide based natural products, like [amphidinolides](#) (*Tetrahedron Lett.* **2001**, 42, 3387-3390; *Curr.Med.Chem. AntiCancer Agents* **2001**, 1, 131-149), [crocacins](#) (*Tetrahedron Lett.* **2001**, 42, 497-499; *Tetrahedron* **2001**, 57, 9461-9467; *Tetrahedron Lett.* **2002**, 43, 2645-2648; *Tetrahedron Lett.* **2003**, 44, 4989-4992), [cruentaren B](#) (*J. Org. Chem.* **2008**, 73, 3578-81), [antascomycin A](#) (*Tetrahedron Lett.* **2006**, 47, 4999-5002; *Tetrahedron Lett.* **2006**, 47, 5003-5005), [stevastelins](#) (*Tetrahedron Lett.* **2001**, 42, 5085-5088; *Tetrahedron Lett.* **2005**, 46, 5445-5448), [clavosolide A](#) (*Tetrahedron Lett.* **2006**, 47, 2099-2102; *Tetrahedron Lett.* **2006**, 47, 7435-7438; *Tetrahedron* **2008**, 64, 5162-5167), [rhizopodin](#), a potent G-actin binding cytostatic polyketide diolide (*Tetrahedron Lett.* **2010**, 51, 6444-6446; *Tetrahedron Lett.* **2011**, 52, 59-61; *Org. Lett.* **2012**, 14, 2858-2861; *Org. Lett.* **2014**, 16, 2284-2287) and many other such molecules.

In fact, in any synthesis of natural products in our laboratory the Ti(III)-mediated epoxide opening is always used as one of the key steps.



Some of the natural products synthesized in our laboratory using Ti(III)-mediated epoxide opening reaction as one of the key steps

Next, we showed that Ti(III)-mediated opening of chiral 2,3-epoxy alcohols followed by intramolecular trapping of the resultant intermediate radicals by a suitably placed electron-deficient double bond leads to the formation of highly functionalized **carbocycles** (Chakraborty, T. K.; Samanta, R.; Das, S. *J. Org. Chem.* **2006**, *71*, 3321–3324), **oxacycles** (Chakraborty, T. K.; Samanta, R.; Ravikumar, K. *Tetrahedron Lett.* **2007**, *48*, 6389–6392) and **azacycles** (Chakraborty, T. K.; Samanta, R.; Roy, S.; Sridhar, B. *Tetrahedron Lett.* **2009**, *50*, 3306–3310).

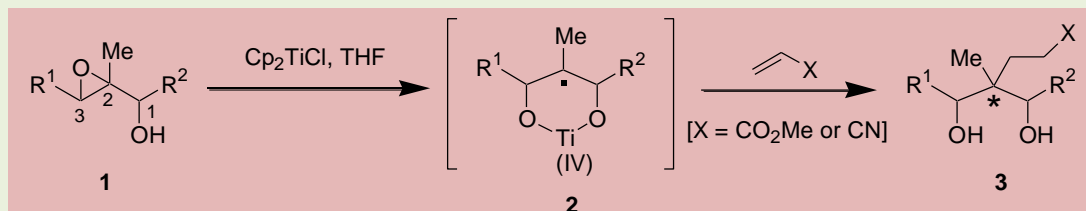


X = CH₂, O, NTs; n = 1,2

[P = H, protective group; R = H, alkyl; R' = Me, Et]

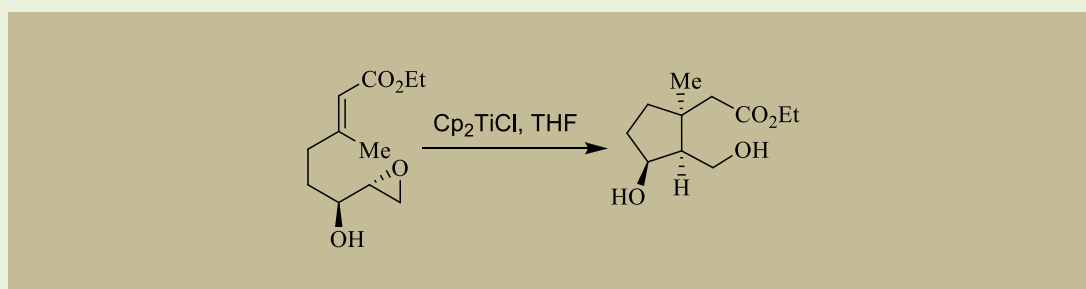
Stereoselective syntheses of highly substituted carbo-, oxa-, and azacycles using Ti(III)-mediated opening of 2,3-epoxy alcohols.

Stereoselective construction of quaternary chiral centres remains a challenging task. A novel method for the same was developed by us using a Ti(III)-mediated opening of chiral 2,3-epoxy alcohols regioselectively at the 2-position followed by trapping of the intermediate radical with methyl acrylate or acrylonitrile to lead to the stereoselective formation of tetrasubstituted chiral centers.



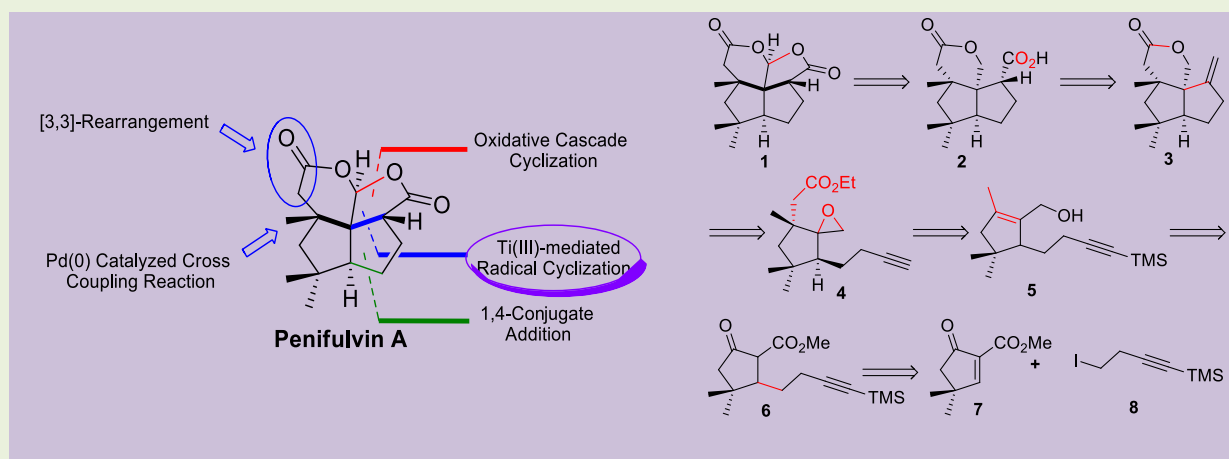
Reference: “Radical-Mediated Opening of 2,3-Epoxy Alcohols Using Cp_2TiCl : Stereoselective Construction of Quaternary Chiral Centers” Tushar Kanti Chakraborty,* Rajarshi Samanta, and Sanjib Das *J. Org. Chem.* **2006**, *71*, 3321-3324.

In a subsequent study on stereoselective construction of quaternary chiral centres, a trisubstituted α,β -unsaturated ester moiety was suitably placed in a molecule also bearing an epoxy alcohol moiety at its other end to intramolecularly trap the intermediate radical, which was formed when the molecule was treated with $\text{Cp}_2\text{Ti(III)Cl}$ to regio- and stereoselectively open its epoxy ring, giving rise to a quaternary chiral center.



Reference: “Stereoselective construction of quaternary chiral centers using Ti(III)-mediated opening of 2,3-epoxy alcohols: studies directed toward the synthesis of penifulvins” Tushar Kanti Chakraborty, Amit Kumar Chattopadhyay, Rajarshi Samanta and Ravi Sankar Ampapathi *Tetrahedron Letters* **2010**, *51*, 4425–4428.

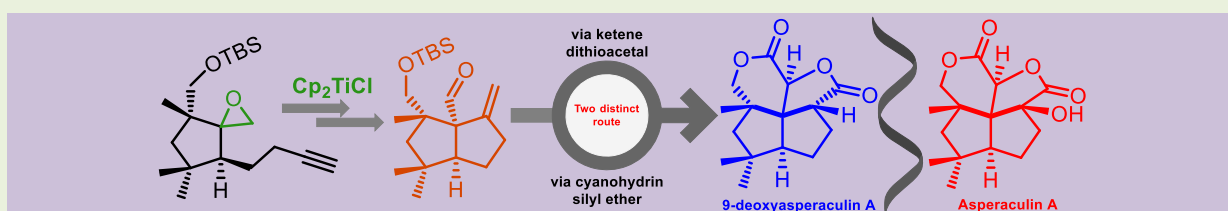
A method that was originally developed by us for the synthesis of polyketide based natural products is found today equally effective in the synthesis of structurally complex terpenes.



Reference: “An Approach to a Bislactone Skeleton: A Scalable Total Synthesis of (\pm)-Penifulvin A” Dipendu Das, Ruchir Kant and Tushar Kanti Chakraborty *Org. Lett.* **2014**, *16*, 2618-2621.

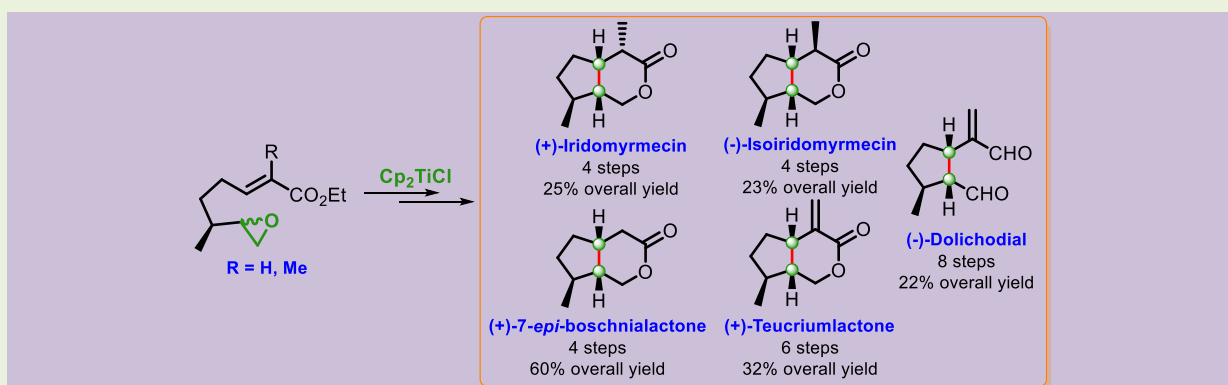
An architecturally challenging sesquiterpenoid penifulvin A having a highly complex dioxo[5.5.5.6]fenestrane skeleton has recently been synthesized in our laboratory using a Ti(III)-mediated epoxide opening followed by a concomitant radical cyclization reaction to stereoselectively construct the most important central quaternary centre of the molecule.

After successful completion of the synthesis of penifulvin A, synthesis of another marine-derived sesquiterpenoid fungal metabolite, asperaculin A, a novel dioxo[5.5.5.6]fenestrane, was undertaken. Two distinct lactonization sequences from a common intermediate led to the first synthesis of 9-deoxyasperaculin A in 14 steps (16% overall yield) and 16 steps (18% overall yield), respectively. [2,3]-Wittig-Still rearrangement and Ti(III)-mediated epoxide opening-cyclization were employed as some of the key steps for the stereoselective generation of the vicinal all-carbon quaternary centers of the target molecule.



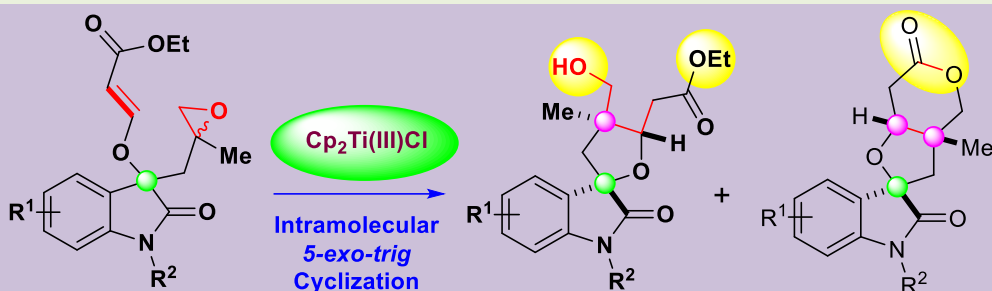
Reference: “Radical Approach to the Chiral Quaternary Center in Asperaculin A: Synthesis of 9-Deoxyasperaculin A” Dipendu Das and Tushar Kanti Chakraborty *Org. Lett.* **2017**, *19*, 682-685.

An expedient approach toward the unified total syntheses of (+)-iridomyrmecin, (-)-isoiridomyrmecin, (+)-7-epiboschnialactone, (+)-teucriumlactone, and (-)-dolichodial in chirally pure forms starting from readily available (+)- β -citronellene has been developed using a Ti(III)-mediated reductive epoxide opening-cyclization for the construction of the core cyclopenta[c]pyran skeleton of the iridoid lactones with complete diastereoselectivity for the newly created bridgehead stereogenic centers. Subsequent transformations gave a short access to (+)-teucriumlactone and (-)-dolichodial and formal access to potentially other iridoids.



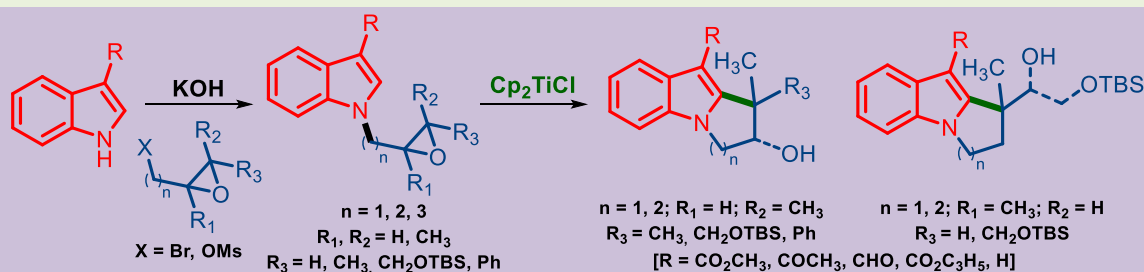
Reference: “Application of Cp_2TiCl -Promoted Radical Cyclization: A Unified Strategy for the Syntheses of Iridoid Monoterpenes” Hina P. A. Khan, Dipendu Das, and Tushar Kanti Chakraborty *J. Org. Chem.* **2018**, *83*, 6086–6092.

An isatin-derived and 3,3-disubstituted oxindole-appended epoxy-acrylate underwent $Cp_2Ti(III)Cl$ -mediated reductive oxirane-ring opening with concomitant intramolecular 5-exo-trig radical cyclization leading to tetrahydrofuran based oxa-spirooxindole systems.



Reference: "Titanocene(III)-Mediated 5-*exo-trig* Radical Cyclization: *en route* to Spirooxindole Based Tetrahydrofuran and Bicyclic Lactone" Jothi Lakshmi Nallasivam and Tushar Kanti Chakraborty *J. Org. Chem.* **2019**, *84*, 16124-16138.

An efficient and novel route for assembling pyrrolo/piperido[1,2-*a*]indoles has been developed involving a Ti(III)-mediated reductive epoxide opening reaction of *N*-tethered epoxy-indoles that triggered facile intramolecular cyclization followed by an oxidative quenching step.



Reference: "Application of Cp₂TiCl-Promoted Radical-Induced Cyclization: An Expedient Access to [a]-Annelated Indoles" Hina P. A. Khan and Tushar Kanti Chakraborty *J. Org. Chem.* **2020**, *85*, 8000-8012.