

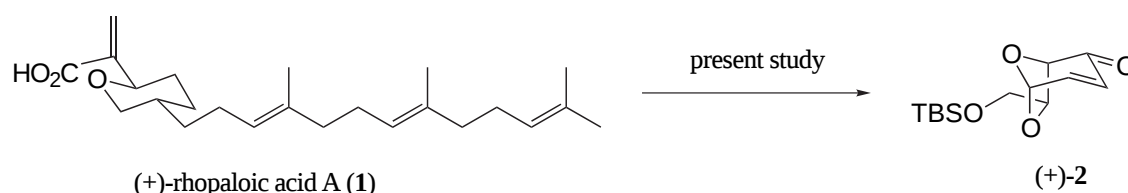
A STEREOCONTROLLED SYNTHESIS OF (+)-RHOPALOIC ACID A USING A DIOXABICYCLO[3.2.1]OCTANE CHIRAL BUILDING BLOCK⁺

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Abstract – Utilizing a chiral building block having a dioxabicyclo[3.2.1]octane framework, (+)-rhopaloic acid A, a potent cytotoxic norsesterterpene isolated from the marine sponge *Rhopaloeides* sp., has been synthesized in a stereocontrolled manner.

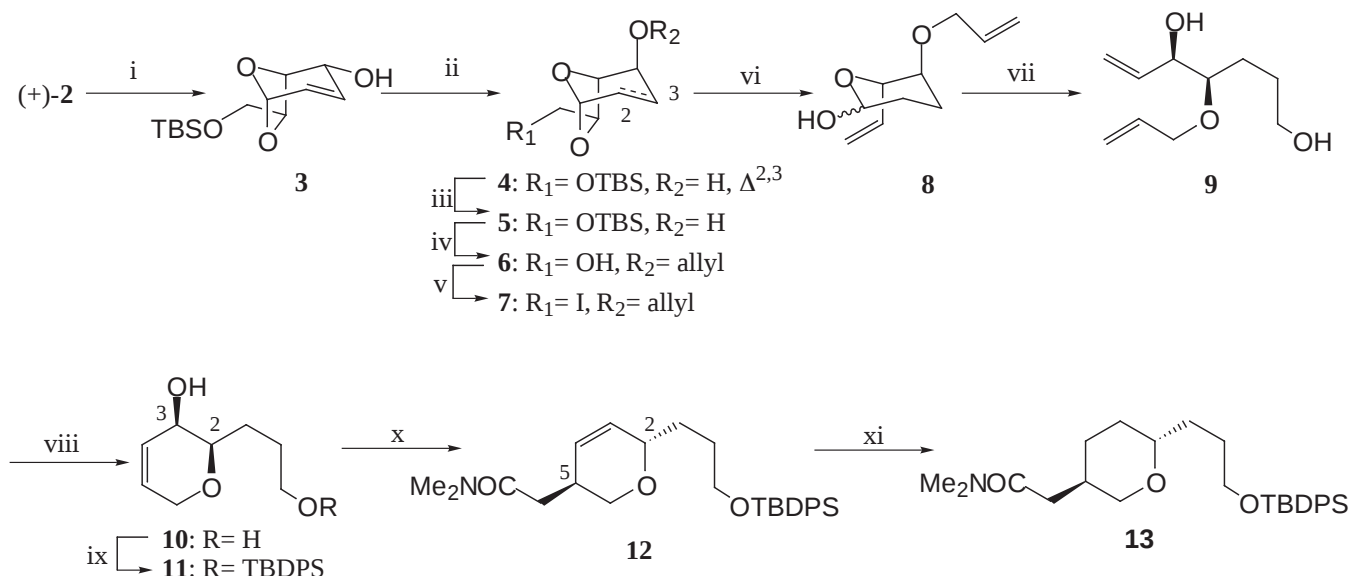
We have developed an efficient preparation of the chiral building block (**2**) having a dioxabicyclo[3.2.1]octane framework in both enantiomeric forms by employing either the Sharpless asymmetric dihydroxylation¹ or the lipase-mediated kinetic resolution² as the key step. This chiral building block (**2**) exhibits inherent convex-face selectivity owing to its sterically biased framework to allow diastereocontrolled construction of a variety of biologically active natural products.³ To extend the versatility of the chiral building block (**2**), we attempted the stereocontrolled synthesis of (+)-rhopaloic acid A (**1**), a potent cytotoxic norsesterterpene having a *trans*-2,5-disubstituted tetrahydropyran core isolated from the marine sponge *Rhopaloeides* sp.^{4,5} We wish to report here the successful stereocontrolled transformation of the chiral building block ((+)-**2**) into (+)-rhopaloic acid A (**1**) based on its stereochemical and chemical backgrounds (Scheme 1).



Scheme 1

We first carried out the construction of the *trans*-2,5-disubstituted tetrahydropyran core of the target molecule. Thus, the enantiopure enone (+)-**2**^{1,2} was transformed into the *exo*-allyl alcohol (**4**), $[\alpha]_D^{27} +119^\circ$ (*c* 1.0, CHCl₃), via the *endo*-allyl alcohol (**3**), $[\alpha]_D^{30} -2.8^\circ$ (*c* 1.1, CHCl₃), by sequential convex-

face selective 1,2-reduction and the Mitsunobu inversion employing previously established procedure.⁶ After catalytic hydrogenation of the olefin moiety of the allyl alcohol (**4**), the resulting alcohol (**5**), $[\alpha]_D^{26} -37.1^\circ$ (*c* 1.0, CHCl_3), was transformed into the allyl ether of which silyl ether moiety was then removed to give the primary alcohol (**6**), $[\alpha]_D^{26} -78.4^\circ$ (*c* 1.0, CHCl_3). To cleave the dioxolane moiety, the alcohol (**6**) was transformed into the iodide (**7**), $[\alpha]_D^{25} +0.1^\circ$ (*c* 1.1, CHCl_3), *via* the mesylate. Upon reductive treatment with zinc powder in methanol containing acetic acid, the iodide (**7**) gave the δ -lactol (**8**), as an epimeric mixture, which was immediately reduced with sodium borohydride to give the acyclic dihydroxydiene (**9**), $[\alpha]_D^{27} +3.6^\circ$ (*c* 0.9, CHCl_3). Ring-closing metathesis⁷ of the diene (**9**) in the presence of a catalytic amount of Grubbs' reagent⁸ afforded the expected diol (**10**) having a 2,3-*trans*-disubstituted dihydropyran framework. Transfer of the *trans*-2,3-stereochemistry of the product (**10**) to the *trans*-2,5-stereochemistry required for the target molecule was next carried out by employing the Eschenmoser rearrangement.⁹ Since the Eschenmoser rearrangement of the diol (**10**) generated a complex mixture of products, its primary hydroxyl functionality was selectively protected to give the *tert*-butyldiphenylsilyl (TBDPS) ether (**11**), $[\alpha]_D^{26} -19.0^\circ$ (*c* 0.9, CHCl_3), leaving the secondary allyl hydroxyl functionality intact. When the TBDPS ether (**11**) was heated with *N,N*-dimethylacetamide dimethyl acetal in diphenyl ether at reflux ($\sim 280^\circ\text{C}$), a clean reaction took place to give the 2,5-*trans*-disubstituted dihydropyran



Scheme 2 *Reagents and conditions*: i) $\text{NaBH}_4\text{-CeCl}_3\cdot 7\text{H}_2\text{O}$, MeOH (99%). ii) HCO_2H , *i*- $\text{PrO}_2\text{CN}=\text{NCO}_2\text{Pr-}i$, PPh_3 , THF, then K_2CO_3 , MeOH (70%). iii) H_2 , PtO_2 , AcOEt (91%). iv) allyl bromide, NaH, THF-DMF (1:1), then Bu_4NF , THF (92%). v) Ms-Cl, Et_3N , CH_2Cl_2 , then LiI, THF, reflux (94%). vi) Zn, AcOH-MeOH (1:9) (97%). vii) NaBH_4 , EtOH (92%). viii) Grubbs' catalyst, CH_2Cl_2 , 40°C . ix) TBDPS-Cl, imidazole, DMF (91%, 2 steps). x) $\text{Me}_2\text{NC(OMe)}_2\text{Me}$, Ph_2O , reflux (92%). xi) H_2 , 10% Pd-C, AcOEt (91%).

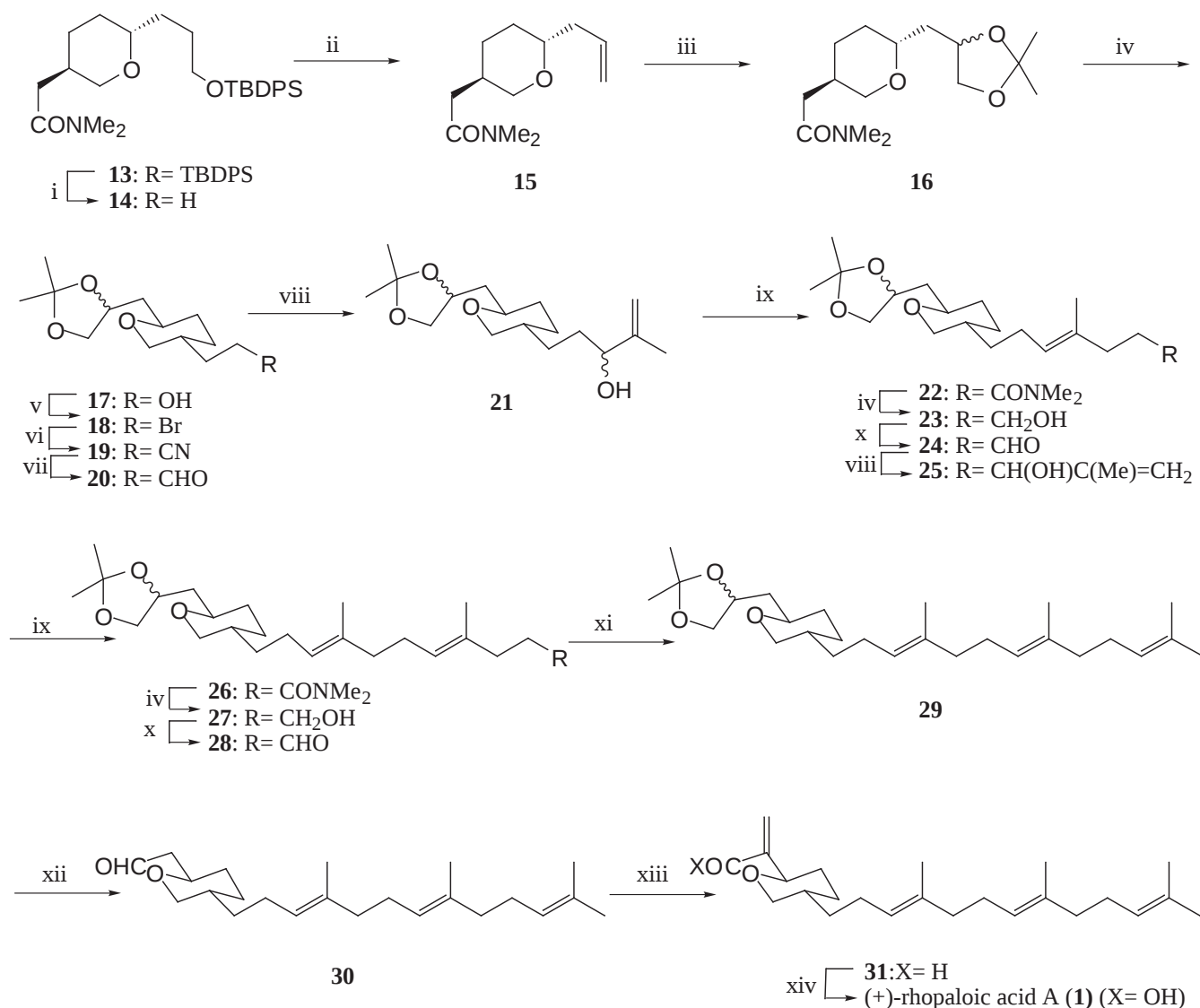
(**12**), ¹⁰ $[\alpha]_{\text{D}}^{25} +56.2^{\circ}$ (c 1.1, CHCl₃), which afforded the tetrahydropyran (**13**), $[\alpha]_{\text{D}}^{26} +10.3^{\circ}$ (c 1.0, CHCl₃), having the requisite stereochemistry on catalytic hydrogenation. The overall yield of the tetrahydropyran core (**13**) from the starting chiral building block ((+)-**2**) was 37% (Scheme 2).

Having constructed the *trans*-2,5-disubstituted tetrahydropyran core (**13**) of the target molecule (**1**), we next carried out transformation of its 2,5-functionalities into the actual functionalities of the target natural product (**1**), respectively. Thus, one extra oxygen atom was first introduced on the C-2 functionality to give the dioxolane (**16**) to prepare for the final construction of the C-2 functionality *via* the primary alcohol (**14**), $[\alpha]_{\text{D}}^{24} +11.7^{\circ}$ (c 1.1, CHCl₃), and the 2-allyl intermediate (**15**) by sequential desilylation, the Grieco dehydration,¹¹ dihydroxylation and ketalization.

We then carried out the construction of the C-5 triene moiety of the target molecule at this stage. Stereocontrolled introduction of the two *E*-trisubstituted olefins in the C-5 functionality was carried out by employing the methodology developed by Johnson and co-workers¹² in the synthesis of squalene but using *N,N*-dimethylacetamide dimethyl acetal under neutral conditions in place of triethyl orthoacetate which was used in the Johnson synthesis in the presence of an acid catalyst. Thus, the tertiary amide (**16**) was transformed into the primary alcohol (**17**) in one step on treatment with lithium triethylborohydride (Super Hydride) in THF.¹³ Under standard conditions the hydroxyl functionality was replaced by the cyano functionality *via* the bromide¹⁴ (**18**) and the resulting cyanide (**19**) was transformed into the aldehyde (**20**) by partial reduction with diisobutylaluminum hydride (DIBAL). Treatment of the aldehyde (**20**) with isopropenylmagnesium bromide in THF afforded the allyl alcohol (**21**) which was heated with *N,N*-dimethylacetamide dimethyl acetal in diphenyl ether at reflux to give the γ,δ -unsaturated amide (**22**) having *E*-configuration¹² selectively through a [3,3] sigmatropic rearrangement.⁹ The resulting tertiary amide (**22**) was then transformed into the enal (**24**) *via* the primary alcohol (**23**) by sequential reduction with lithium triethylborohydride¹⁴ and the Swern oxidation.¹⁴ Upon the reiteration of the same four steps of sequence above involving the Grignard reaction, the Eschenmoser [3,3] sigmatropic rearrangement, the lithium triethylborohydride-mediated reduction and the Swern oxidation, the aldehyde (**24**) furnished the dienal (**28**) as the single product *via* the allyl alcohol (**25**), the tertiary amide (**26**) and the primary alcohol (**27**). Finally, the aldehyde (**28**) was treated with the Wittig reagent to give the triene (**29**) to complete the installation of the C-5 functionality.

To complete the synthesis of the target natural product, the dioxolane moiety of the triene (**29**) thus obtained was hydrolyzed at this stage under acidic conditions to generate the 1,2-glycol which was cleaved with sodium periodate to give the aldehyde (**30**), $[\alpha]_{\text{D}}^{31} +7.5^{\circ}$ (c 0.5, CHCl₃). Upon treatment with dimethylmethyleammonium chloride¹⁶ in dichloromethane in the presence of triethylamine, the aldehyde (**30**) furnished the α -methylidene aldehyde (**31**), $[\alpha]_{\text{D}}^{29} +40.6^{\circ}$ (c 0.5, CHCl₃), by concurrent

Mannich and elimination reactions as expected on the basis of our previous observation.¹⁷ Finally, the α,β -unsaturated aldehyde (**31**) was oxidized¹⁸ to afford the target natural product (–)-rhopaloic acid **1** (**1**), $[\alpha]_D^{29} +41.3^\circ$ (*c* 0.2, CHCl_3)¹⁹{natural⁴: $[\alpha]_D^{25} +40^\circ$ (*c* 0.47, CHCl_3)}. The overall yield of the natural product from the tetrahydropyran intermediate (**13**) was 5%, and, thus, 2% from the starting chiral building block ((+)-**2**) (Scheme 3).



Scheme 3 *Reagents and conditions*: i) Bu_4NF , THF (100%). ii) $o\text{-(NO}_2\text{)}_2\text{C}_6\text{H}_4\text{SeCN}$, Bu_3P , THF, then 30% H_2O_2 , THF. iii) OsO_4 (cat.), NMO, 50% aq. THF, then $\text{Me}_2\text{C(OMe)}_2$, PPTS, toluene, 100°C (70%, 4 steps). iv) LiEt_3BH , THF, -30°C (95%). v) NBS, PPh_3 , pyridine, CH_2Cl_2 (88%). vi) KCN, DMSO (100%). vii) DIBAL, CH_2Cl_2 , $-78\sim 0^\circ\text{C}$, aqueous workup (84%). viii) isopropenyl-MgBr, THF, $-78\sim -40^\circ\text{C}$. ix) $\text{Me}_2\text{NC(OMe)}_2\text{Me}$, Ph_2O , reflux (55% for **22**; 56% for **26**, 2 steps). x) LiEt_3BH , THF, $-30\sim 0^\circ\text{C}$, then Swern oxidation (76% for **24**; 75% for **28**, 2 steps). xi) $i\text{-PrPPh}_3\text{I}$, BuLi, THF, 0°C (63%). xii) $\text{CF}_3\text{CO}_2\text{H}$, 20% aq. THF, then NaIO_4 , 50% aq. THF (97%). xiii) $\text{CH}_2=\text{NMe}_2\text{Cl}$, Et_3N , CH_2Cl_2 (93%). xiv) NaClO_2 , NaH_2PO_4 , 2-methylbut-2-ene, 90% aq. *t*-BuOH (96%).

In conclusion, we have demonstrated a new utilization of our dioxabicyclo[3.2.1]octane chiral building block by a stereocontrolled synthesis of a potent cytotoxic norsesiterpene (–)-rhopaloidic acid isolated from the marine sponge *Rhopaloeides* sp. using the (+)-enantiomer and have extended the versatility of our chiral building block.

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+ Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

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