HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 485 - 490, Received, 17th September, 2002

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

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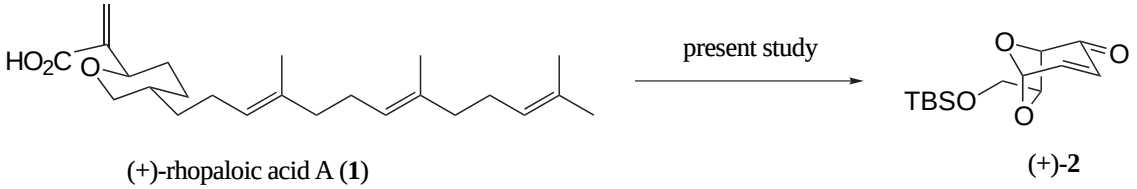
Abstract – Utilizing a chiral building block having a dioxabicyclo[3.2.1]octane framework, (+)-rhopaloic acid A, a potent cytotoxic norsesterterpene isolated from the marine sponge *Rhopaloeides* sp., has been synthesized in a stereocontrolled manner.

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 dihydroxylation[1] or the lipase-mediated kinetic resolution[2] 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).

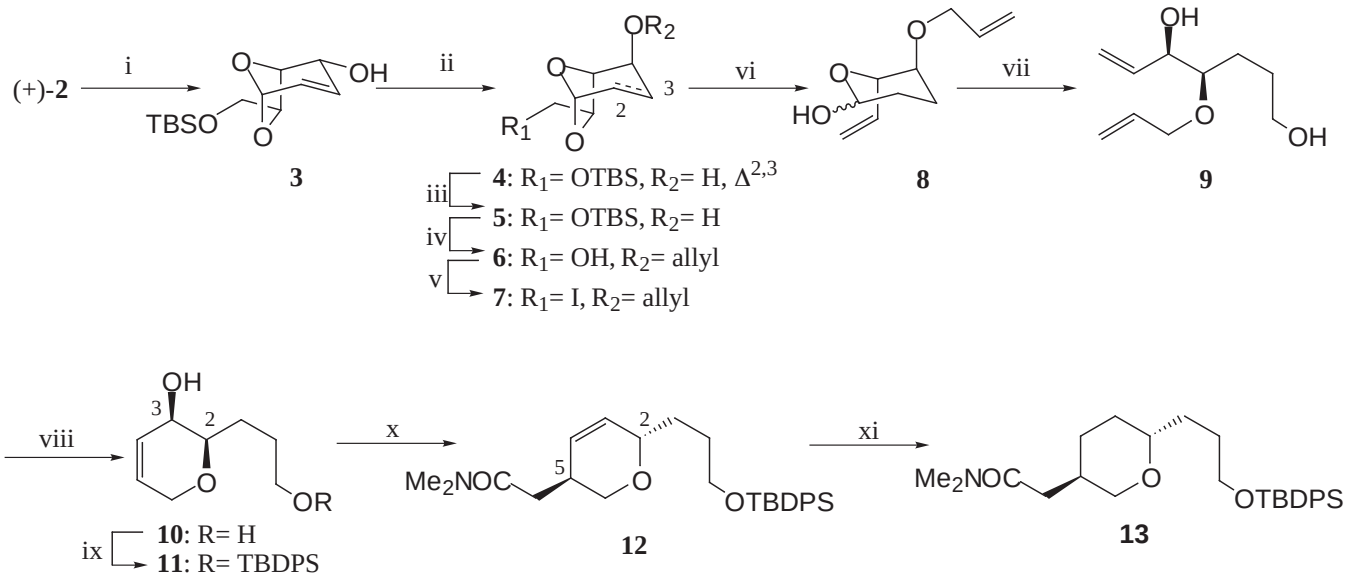


(+)-rhopaloic acid A (**1**) (+)-**2**

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° (*c* 1.0, $CHCl_3$), *via* the *endo*-allyl alcohol (**3**), $[\alpha]_D^{30}$ –2.8° (*c* 1.1, $CHCl_3$), 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° (*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° (*c* 1.0, $CHCl_3$). To cleave the dioxolane moiety, the alcohol (**6**) was transformed into the iodide (**7**), $[\alpha]_D^{25}$ +0.1° (*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° (*c* 0.9, $CHCl_3$). Ring-closing metathesis[7] of the diene (**9**) in the presence of a catalytic amount of Grubbs' reagent[8] 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-stereochemisty 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° (*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 (~280 °C), a clean reaction took place to give the 2,5-*trans*-disubstituted dihydropyran



Scheme 2 *Reagents and conditions*: i) $NaBH_4$-$CeCl_3$-$7H_2O$, MeOH (99%). ii) HCO_2H, *i*-$PrO_2CN{=}NCO_2Pr$-*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) $Me_2NC(OMe)_2Me$, Ph_2O, reflux (92%). xi) H_2, 10% Pd-C, AcOEt (91%).

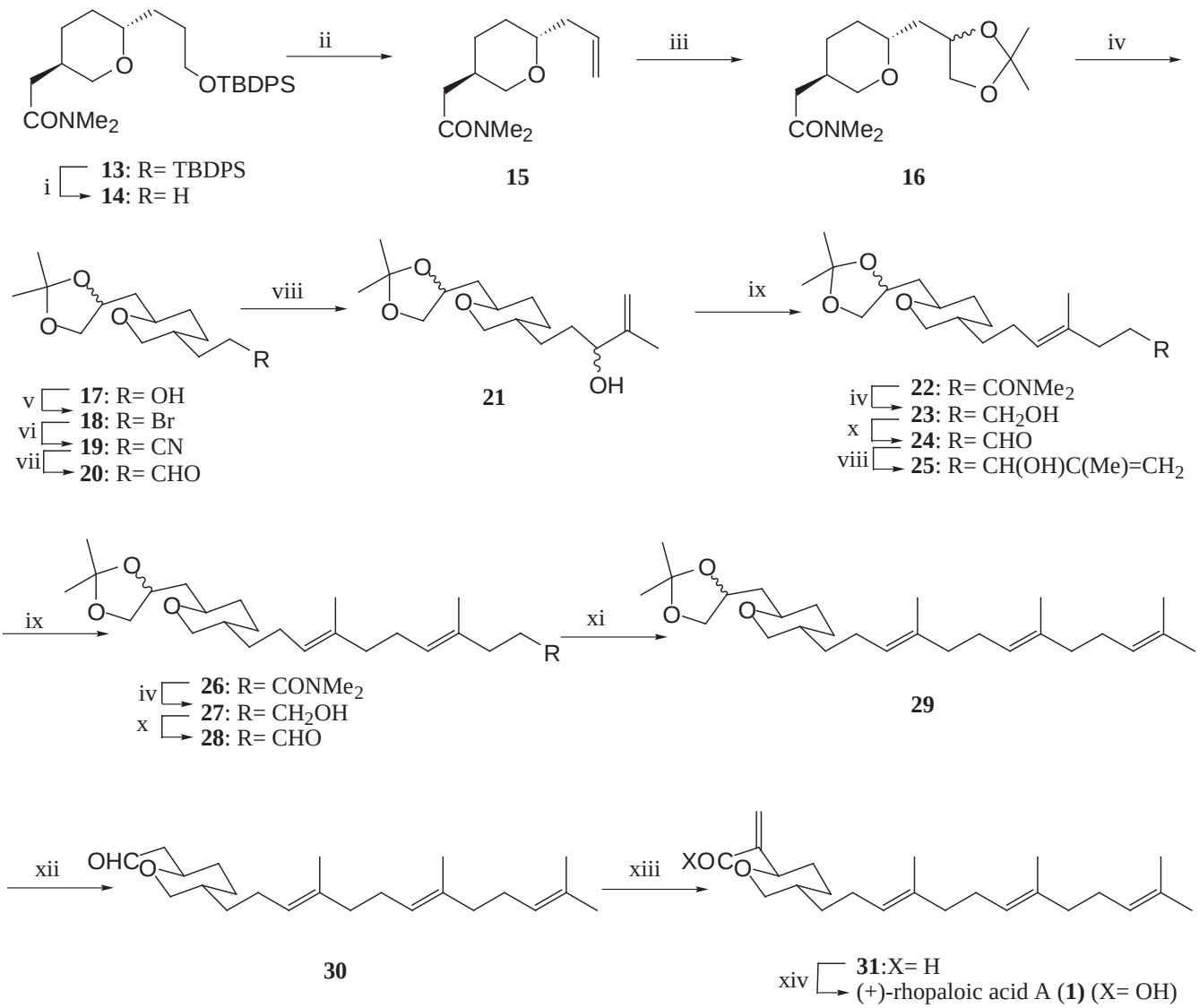
(**12**), [10] $[\alpha]_D^{25}$ +56.2° (*c* 1.1, $CHCl_3$), which afforded the tetrahydropyran (**13**), $[\alpha]_D^{26}$ +10.3° (*c* 1.0, $CHCl_3$), having the requisite stereochemistry on catalytic hydrogenation. The overall yield of the tetrahydropyran core (**13**) from the starting chiral building 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**), $[\alpha]_D^{24}$ +11.7° (*c* 1.1, $CHCl_3$), 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-workers[12] 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 bromide[14] (**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*-configuration[12] 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 triethylborohydride[14] 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**), $[\alpha]_D^{31}$ +7.5° (*c* 0.5, $CHCl_3$). Upon treatment with dimethylmethyleneammonium chloride[16] in dichloromethane in the presence of triethylamine, the aldehyde (**30**) furnished the α-methylidene aldehyde (**31**), $[\alpha]_D^{29}$ +40.6° (*c* 0.5, $CHCl_3$), by concurrent

Mannich and elimination reactions as expected on the basis of our previous observation.[17] Finally, the α,β-unsaturated aldehyde (**31**) was oxidized[18] to afford the target natural product (–)-rhopaloic acid A (**1**), $[\alpha]_D^{29}$ +41.3° (*c* 0.2, $CHCl_3$)[19]{natural[4]: $[\alpha]_D^{25}$ +40° (*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*-$(NO_2)C_6H_4SeCN$, Bu_3P, THF, then 30% H_2O_2, THF. iii) OsO_4(cat.), NMO, 50% aq. THF, then $Me_2C(OMe)_2$, 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, –78~0 °C, aqueous workup (84%). viii) isopropenyl-MgBr, THF, –78~–40 °C. ix) $Me_2NC(OMe)_2Me$, Ph_2O, reflux (55% for **22**; 56% for **26**, 2 steps). x) $LiEt_3BH$, THF, –30~0 °C, then Swern oxidation (76% for **24**;75% for **28**, 2 steps). xi) *i*-$PrPPh_3I$, BuLi, THF, 0 °C (63%). xii) CF_3CO_2H, 20% aq.THF, then $NaIO_4$, 50% aq.THF (97%). xiii) $CH_2=NMe_2Cl$, 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]octnane chiral building block by a stereocontrolled synthesis of a potent cytotoxic norsesterterpene (–)-rhopaloic acid isolated from the marine sponge *Rhopaloeides* sp. using the (+)-enantiomer and have extended the versatility of our chiral building block.

ACKNOWLEDGEMENTS

We are grateful to the Ministry of Education, Culture, Sports, Science and Technology, Japan for support of this work. We thank Professor Yoshiharu Iwabuchi, Pharmaceutical Institute, Tohoku University, for helpful suggestions.

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

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