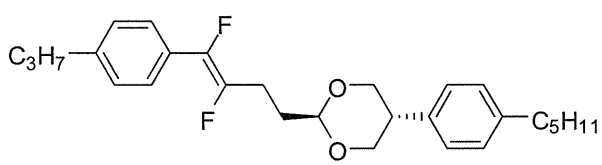
100ml のナスフラスコに 2-(4-pentylphenyl)- propane-1,3-diol (0.32g, 1.4mmol)、トシル酸（一水和物）(0.008g, 0.04mmol)、THF 5.0ml を入れよく撹拌させた。そこに 1,1-dimethoxy-3-bromopropane (0.31 g, 1.7mmol) を少しずつ加え、50℃で 12 時間撹拌した。トリエチルアミンでクエンチした後に Et_2O で抽出した。エバポレーターを用いて濃縮した粗生成物から、カラムクロマトグラフィー（ヘキサン：酢酸エチル＝7：1)、続くカラムクロマトグラフィー（ヘキサン：塩化メチレン＝2：1）により目的物を得た。 収率 70%
白色固体

^{1}H-NMR($CDCl_3$, 300MHz) δ 0.77-0.82(m, 3H), 1.12-1.24(m, 4H), 1.44-1.54(m, 2H), 2.09-2.17(q, 2H), 2.47(t, 2H), 3.00-3.11(m, 1H), 3.37-3.42(t, 2H), 3.66-3.74(t, 2H), 3.98-4.09(dd, 2H), 4.70 (t, 1H), 6.88-7.10 (q, 4H)

^{13}C-NMR ($CDCl_3$, 300 MHz) δ 14.14, 14.30, 22.62, 27.89, 31.23, 31.59, 35.61, 37.93, 40.92, 71.99, 99.91, 127.57, 128.84, 134.70, 142.19

(2r,5r)-2-((*E*)-3,4-Difluoro-4-(4-propylphenyl)but-3-enyl)-5-(4-pentylphenyl)-1,3-dioxane



乾燥させた２口ナスフラスコを Ar 置換し、
(2r,5r)-2-(2-bromoethyl)-5-(4-pentylphenyl)-1,3-dioxane (0.22 g, 0.64 mmol)、dry Et_2O 13ml を - 78℃で撹拌した。そこに *t*-BuLi(0.85 ml, 1.35 mmol)をゆっくりと滴下し、- 78℃で 30 分間、- 40℃で 10 分間撹拌した。次に-40℃でトリフルオロ体 **3** (0.14 g, 0.71 mmol) を滴下した。２時間後、HCl (1N) 溶液を加え、Et_2O で抽出し、エバポレーターを用いて濃縮した粗生成物から、カラムクロマトグラフィー（ヘキサン：酢酸エチル＝14：1)、続くカラムクロマトグラフィー（ヘキサン：塩化メチレン＝2：1）により目的物を得て、再結晶（EtOH、－40 ℃）でさらに精製した。収率 44%(*trans*) 白色固体

IR(KBr) 3331, 2953, 2928, 2855, 1693, 1626, 1515, 1466, 1215, 1141, 1100, 1048, 974, 824, 593 cm^{-1}

^{1}H-NMR($CDCl_3$, 300MHz) δ 0.86-0.97(m, 6H), 1.31-1.32(m, 4H), 1.53-1.67(m, 4H), 1.96-2.02(m, 2H), 2.53-2.76(m, 6H), 3.19(m, 1H), 3.80(t, 2H), 4.19(dd, 2H), 4.69(t, 1H), 7.10(q, 6H), 7.53(d, 2H)

^{19}F-NMR ($CDCl_3$, 376 MHz) δ -157.85(d, J = 122.0, 6.1 Hz, 1F), -147.53(dt, J = 122.0, 24.4 Hz, 1F)

^{13}C-NMR ($CDCl_3$,100 MHz) δ 13.82, 14.06, 22.46, 22.55, 24.45, 31.18, 31.53, 35.5
4, 37.83, 40.83, 72.02, 100.85, 125.11, 125.22, 127.54, 128.50, 128.77, 134.76, 142.17

F. 研究発表

2. 学会発表

井上誠一、江川 良、星野雄二郎、本田 清、ジフルオロ-1-ブテン骨格を有する化合物の高 Tc 化、第１６回液晶化学研究会シンポジウム、神奈川、2012.5.18.

ジフルオロ-1-ブテン骨格を有する化合物の高 Tc 化

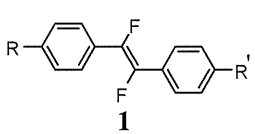
(横国大院環境情報) 井上誠一・○江川良・星野 雄二郎・本田清

【概要】

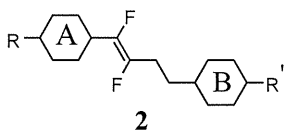
トリフルオロエチレン化合物と有機リチウム試薬による付加脱離反応によってジフルオロ-1-ブテン骨格を有する化合物を合成した。構造と物性の関係を明らかにする目的で今回はジオキサン環、ピリミジン環を有する二環式化合物及び炭素環三環式化合物を合成して物性を比較した。

1. 背景および目的

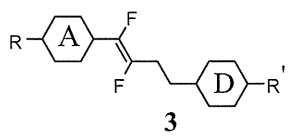
当研究室では、ジフルオロスチルベン化合物（DFS）**1** が低粘性かつ高屈折率異方性という液晶化合物として有用な物性を示すことを見出している [1]。しかし、DFS は液晶性を持たない *cis* 体への光異性化という問題があった。長い共役系をなくすことでその問題を解決するために、ジフルオロ-1-ブテン化合物 2 を合成したが、液晶としての物性は満足のいくものではなかった [2]。そこで、分子長軸方向に双極子モーメントを持つ複素環を導入するか、三環式にすることによって分子の高 Tc 化を狙うことにした。



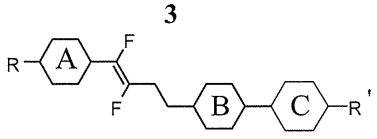
1



2



3

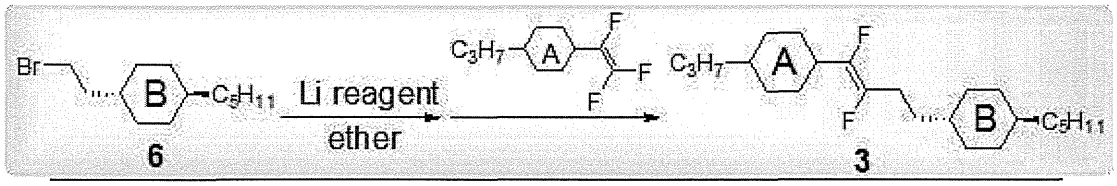


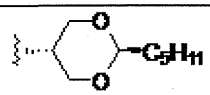
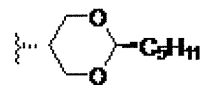
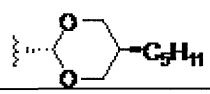
4

R, R' = C_3H_7 or C_5H_{11} A, B, C = C_6H_4 or C_6H_{10} D = dioxane or pyrimidine

2. ジオキサン型化合物の合成

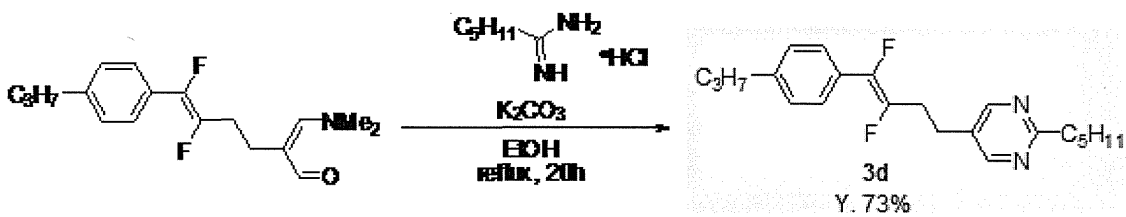
マロン酸ジエチル、ブロモ酢酸エチル、及びヘキサナールを原料として合成したブロモ体 **6** からジオキサン環 **3a** 及び **3b** を合成した。また、ペンチルマロン酸ジエチルを出発原料として合成したブロモ体 **6** からジオキサン型化合物 **3c** を合成した。



A	B	Li reagent	temp. (°C)	product	yield
C_6H_{10}		Li	0	3a	60%
C_6H_4		Li	-12	3b	38%
C_6H_4		t-BuLi	-70→-10	3c	50%

3. ピリミジン型化合物の合成

トリフルオロエチレン化合物から 4 炭素伸長し、ヘキサンアミジンを用いて、良好な収率でピリミジン型化合物 3d を合成した。



4. 物性測定

得られた化合物について、物性を測定した。DSC 以外の測定値は外挿値を記載している（測定濃度は約 10%とした）。

化合物	相転移 (DSC) 昇温	降温	Tc / ℃	η_r/mPa・s (0℃)	Δn
3a	C 64 I	-	-42.9	134.1	0.044
3b	C 54 I	-	-20.1	119.9	0.076
3c	C 37 I	I 33 N 27 I	40.8	137.3	0.115
3d	C 49 I	-	-54.5	164.8	0.102
2a	C 31 I	-	-20.7	13.6	0.151

ジオキサン型化合物 **3b** と **3c** の比較から、酸素原子が分子内側にあるものは液晶性を示し、高 Tc であることを確認できた。**3d** は低 Tc、高粘性となったが、ピリミジン環を有する液晶化合物は窒素原子が分子内側にあるものが多く報告されているので[3]、今後そのような化合物の合成も目指す。

5. 三環式化合物の合成

Trans,trans-4'-ペンチルビシクロヘキサン-4-カルボン酸及び 1-ヨード-4-(*trans*-4-ペンチルシクロヘキシル)ベンゼンを出発原料として 1 炭素伸長、ハロゲン化することでハロゲン化合物 **5** を合成した。**5** から調製されたリチウム試薬を、トリフルオロエチレン化合物に反応させることで高収率かつ高立体選択的に目的物 **4** を得ることができた(4d の反応条件は検討中)。

6. 物性測定

化合物	相転移 (DSC)	Tc / ℃	η_r/mPa・s (0℃)	Δn
4a	C 70 Sm 98 N 119 I	112	112.4	0.108
4b	C 63 Sm 88 N 136 I	131	67.25	0.185
4c	C 9.5 Sm 21 Sm 157 N 176 I	173	115	0.149

二環式化合物 **2** から三環式化合物 **4** にすることで、期待していたように高 Tc 化を確認できた。ただし、粘性も上昇してしまったので、さらなる検討の余地があると考えられる(4d の物性値は測定中である)。

【参考文献】

1) 井上誠一、町田勝利、染料と薬品 **41**(3)、57(1996)
2) 井上誠一ら、第 14 回液晶シンポジウム講演要旨集 p.12 (2010)
3) 加藤隆史ら、「液晶便覧」液晶便覧編集委員会(2001)

G．研究発表

1. 論文発表

1.1. Y. Hoshino, M. Oyaizu, Y. Koyanagi, K. Honda, *Synthetic Communications* **2013**, *43*, 2484-2492.

Enantiomerically Enriched Bicyclic Hydroxamic Acids in One Step from ・ -Aminohydroxamic Acids and Keto Acids via Cyclocondensation

Abstract: New enantiomerically enriched bicyclic hydroxamic acids, 1-hydroxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, have been synthesized by the cyclocondensation of L- ・ -aminohydroxamic acids with keto acids in a highly chemo- and stereoselective manner. The cis configuration between the amino acid side chain and the methyl group at C7a in 1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione was unambiguously established by X-ray crystallographic analysis. This method could also be applied to the cyclocondensation with *o*-formylbenzoic acid, giving a tricyclic hydroxamic acid in a good yield.

Keywords: chiral compounds, hydroxamic acids, cyclocondensation, *N*-hydroxyimidazolidinones, keto acids

INTRODUCTION

Cyclic hydroxamic acids are widely distributed in nature such as siderophores, antibiotics, microbial pigments and exhibit several biological activities, e.g. inhibitory activities of matrix metalloproteinases, human hypoxia-inducible factor (HIF) prolyl hydroxylase, phosphatase, interleukin IL-1 ・ converting enzyme (ICE), and HIV-1 integrase, and antagonistic activity of *N*-methyl-D-aspartate (NMDA) receptor, immunosuppressing activity, and antimalarial activity.[1-9] The synthetic methods of cyclic hydroxamic acids have attracted the attention of many research groups. One interesting area of research is the cyclocondensation reaction of ・ ・ -aminohydroxamic acids with carbonyl compounds, giving monocyclic hydroxamic acids, 3-hydroxyimidazolidin-4-ones.[10] This cyclocondensation reaction provides a potentially attractive method to stereoselectively prepare the 2,5-disubstituted 3-hydroxyimidazolidin-4-ones, which allows diverse elements to be incorporated at the C2 and C5 positions.

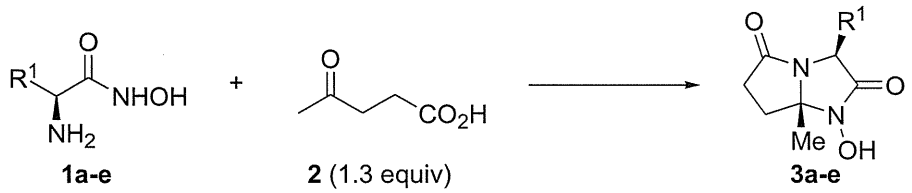
Chiral acyclic hydroxamic acids have recently received increasing attention as a chiral ligand in the field of asymmetric transition-metal catalysis such as epoxidation of alkenols[11] or alkenylsulfonamides[12] or simple olefins[13], oxidation of sulfides,[14] and reduction of ketones[15]. On the other hand, chiral cyclic hydroxamic acids, to the best of our knowledge,

have never been examined as a chiral ligand candidate in asymmetric metal catalysis. The structural diversity of 2,5-disubstituted 3-hydroxyimidazolidin-4-ones makes this compound class convenient for exploration and optimization of chiral cyclic hydroxamic acid ligands and necessitates the development of stereoselective synthesis of such molecules. Although the reaction of glycine hydroxamic acid or some racemic · -aminohydroxamic acids with aldehydes or symmetric ketones have been reported,[10] the examples of diastereoselective cyclocondensation of · -aminohydroxamic acids to 2,5-disubstituted 3-hydroxyimidazolidin-4-ones have been fairly limited and have not indicated the selectivities.[10a-c,h] In addition, the competitive *O*-alkylation of hydroxamic acids may result in the unfavorable formation of 1,2,5-oxadiazinan-3-ones,[10a,16] though *N*-alkylation of amide N-H preferentially occurred in the condensation of · -amino acid phenylhydrazides with levulinic acids and carbonyl compounds.[17] Herein we report the first synthesis of enantiomerically enriched 1-hydroxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, a kind of 2,5-substituted 3-hydroxyimidazolidin-4-one derivatives, by means of the cyclocondensation of L- · -aminohydroxamic acids **1a-e** with levulinic acid (**2**) or 5-oxohexanoic acid (**5**), which has a feature that enables the facile combinatorial synthesis of the libraries of chiral cyclic hydroxamic acids from commercially available or easily prepared · -aminohydroxamic acids and carbonyl compounds. The stereochemistry of (3*S*,7a*R*)-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione **3a** was unambiguously confirmed by X-ray crystallographic analysis. This method also could be applied to the cyclocondensation of · -aminohydroxamic acids with *o*-formylbenzoic acid (**6**).

RESULTS AND DISCUSSION

L- · -Aminohydroxamic acids **1a-e** were prepared in good yields from their respective methyl esters in a similar manner to the literature procedure.[18] When L-phenylalanine hydroxamic acid (**1a**) was treated with levulinic acid (**2**) in refluxing toluene, the sparingly soluble compound **3a**, which gave a positive (purple) color test with ferric chloride, suggesting the presence of a hydroxamic acid function, was obtained in a good yield (Table 1, entry 1). The ^{1}H-NMR analysis of the solid **3a** suggested a 1:1 condensation product of **1a** with **2** but elucidation of the structure was remained ambiguous. The irradiation of CH_3 group of **3a** caused a positive NOE for the Ar-H and had no effect on the hydrogen atom of CH · to the hydroxamic acid moiety (Figure 1). Similarly, irradiation of the benzylic CH_2 led to a positive NOE for the CH_3. These ^{1}H-NMR data provide an evidence for the cis stereochemistry of the CH_3 group to the benzyl group. Finally, the structure of cyclic hydroxamic acid **3a** was established by X-ray diffraction analysis (Figure 2). It is important to note that the reaction

proceeded in a highly chemo- and stereo-selective manner to give exclusively the cis isomer. This stereochemical outcome is comparable to the related cyclization reactions.[17,19] The procedure using Dean-Stark apparatus is also applicable to the condensation, giving the same results (entry 2).



Scheme 1. The cyclocon densation of L- · -aminohydroxamic acids (**1**) with levulinic acid (**2**).

Entry	1	R^1	Conditions	3	Yield (%)
1	**1a**	$PhCH_2$	toluene, reflux, 2h	**3a**	84
2	**1a**		toluene, reflux, 18h (Dean-Stark app.)	**3a**	82
3	**1b**	Me	toluene, 80 ° C, 5h	**3b**	49
4	**1c**	*i*-Pr	toluene, reflux, 4h	**3c**	59
5	**1d**	indol-3-ylmethyl	2-propanol, reflux, 2h; toluene, reflux, 7h	**3d**	95
6	**1e**	imidazol-4-ylmethyl	2-propanol, reflux, 2h; toluene, reflux, 7h	**3e**	96

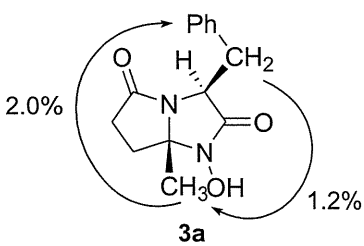


Figure 1. NOE experiment of **3a**.

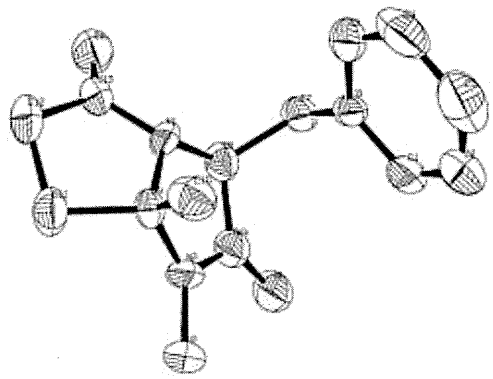
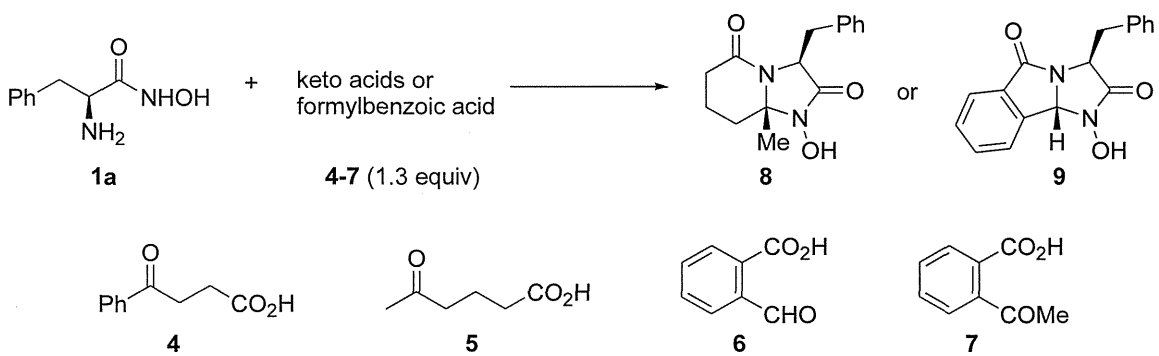


Figure 2. ORTEP diagram of **3a**.

Some representative aminohydroxamic acids were evaluated for cyclocondensation with levulinic acid (Table 1, entries 3-6). Aliphatic aminohydroxamic acids **1b** and **1c** gave the cyclic hydroxamic acids **3b** and **3c** in moderate yields (49-59%). On the other hand, aromatic aminohydroxamic acids **1d** and **1e** were sparingly soluble in toluene and the unknown brown gum substance appeared in the refluxing reaction mixture. Consequently, the condensations of **1d** and **1e** with **2** were carried out in refluxing 2-propanol for 2 h. Then, toluene was added to the reaction mixture, which was heated to 135 ° C while 2-propanol and water were distilled off azeotropically with toluene. This method gave the desired cyclic hydroxamic acids **3d** and **3e** in high yields (95-96%). It is noted that all the products obtained show the cis configuration of methyl group and side chain of aminoacyl moiety.

Next, the possibility to vary the structure of keto acids was examined (Table 2). Phenyl substituted keto acid **4** was conducted in either toluene or 2-propanol, but the desired phenyl-substituted bicyclic hydroxamic acid was not obtained at all, presumably because the first ring closure or the second cyclization might be suppressed by sterically demanded phenyl group. 5-oxohexanoic acid (**5**) was condensed with **1a**, affording the corresponding 5-6 bicyclic hydroxamic acid **8** in a good yield.



Scheme 2. The cyclocondensation of L-phenylalanine hydroxamic acid (**1a**) with oxo acids.

Table 2. Cyclocondensation of L-phenylalanine hydroxamic acid (**1a**) with oxo acids

Entry	Oxo acid	Conditions	Cyclic hydroxamic acid	Yield (%)
1	**5**	toluene, reflux, 7h	**8**	67
2	**6**	toluene, reflux, 20h	**9**	15
3	**6**	p-TsOH (0.1 equiv), toluene, reflux, 20h	**9**	40
4	**6**	p-TsOH (0.1 equiv), xylene, reflux, 20h	**9**	27
5	**6**	p-TsOH (0.1 equiv), benzene, reflux, 20h	**9**	72

To expand this method, benzoic acid derivatives were next examined. While the reaction of formylbenzoic acid **6** with aminohydroxamic acid **1a** in the above reaction conditions gave poor result (Table 2, entry 3), addition of *p*-toluenesulphonic acid (0.1 equiv) as an acid catalyst improved the yield of **9** (40%). Since the white solid intermediate appeared during the reaction, *o*-xylene (140 ° C) was used as solvent in order to dissolve the solid but the yield was not improved. After some trials, use of benzene as solvent and Dean-Stark apparatus for azeotropic distillation resulted in a good yield (72%). The absolute configuration of the newly generated chiral center in **9** was determined by NOE experiments. A similar *trans*-orientation of H3 and H9b was reported in the related condensations by Katritzky et al.[20] For the reaction with *o*-acetylbenzoic acid (**7**), the starting material aminohydroxamic acid was consumed quantitatively, but complex mixtures were obtained. No desired product was observed in spectroscopic analysis.

In summary, we have demonstrated that the cyclocondensation of L- · -aminohydroxamic acids with · - and · -keto acids afforded optically active, sterically rigid bi- or tricyclic hydroxamic acids in a highly chemo- and stereo-selective manner. The simple experimental procedure along with ready accessibility of reactants is also an attracting feature. Application of these cyclic hydroxamic acids to catalytic asymmetric reactions using metal complexes is in progress.

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In summary, we have demonstrated that the cyclocondensation of L- · -aminohydroxamic acids with · · and · -keto acids afforded optically active, sterically rigid bi- or tricyclic hydroxamic acids in a highly chemo- and stereo-selective manner. The simple experimental procedure along with ready accessibility of reactants is also an attracting feature. Application of these cyclic hydroxamic acids to catalytic asymmetric reactions using metal complexes is in progress.

EXPERIMENTAL

A typical experimental procedure for the cyclocondensation of L- · -aminohydroxamic acids (1) with levulinic acid: To a stirred suspension of L-phenylalanine hydroxamic acid (**1a**) (0.326 g, 1.81 mmol) in toluene (30 mL) was slowly added levulinic acid (0.241 mL, 2.35 mmol) at 120 °C. After the reaction mixture was stirred for 2 h at the same temperature, it was carefully concentrated to about 10 mL by evaporation and stood at room temperature overnight. The precipitated white solid was filtrated and washed with diethyl ether to afford bicyclic hydroxamic acid **3a** (0.397 g, 84%). The stereochemistry of **3a** was determined by NOE experiments and X-ray diffraction analysis.

(3*S*, 7a*R*)-3-Benzyl-1-hydroxy-7a-methyl-dihydro-1*H*-pyrrolo[1, 2-*a*]imidazole-2, 5(3*H*, 6*H*)-dione (3a). Colorless crystal; mp 205 °C; R_f 0.35 (ethyl acetate); $[\square]_D^{25}$ +118 (c = 1.0, $CHCl_3$); IR (KBr) 3127, 2928, 2867, 1727, 1700, 1666, 1458, 1332, 702, 574 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) □ 0.99 (s, 3H), 2.17-2.45 (m, 3H), 2.61-2.76 (m, 1H), 3.07 (dd, *J* = 5.9, 13.9 Hz, 1H), 3.16 (dd, *J* = 5.3, 13.9 Hz, 1H), 4.60 (t, *J* = 5.9 Hz, 1H), 7.17-7.32 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) □ 24.0, 30.9, 34.7, 36.9, 58.3, 82.3, 127.1, 128.5, 129.9, 135.9, 168.4, 178.6; Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.34; H, 6.17; N, 10.66.

Crystal Data for 3a: $C_{14}H_{16}N_2O_3$; M = 260.29, colorless block crystals, 0.30 x 0.30 x 0.10 mm, orthorhombic, space group P212121 (No.19), *a* = 11.327(7), *b* = 13.653(6), *c* = 8.520(3) Å, *V* = 1317.(1) $Å^3$, *Z* = 4, *Dc* = 1.31 g cm^{-3}. *F*(000) = 552, □(CuK□) = 0.769 mm^{-1}.

A typical experimental procedure for the cyclocondensation of aromatic L- · -aminohydroxamic acids (1) with levulinic acid: To a stirred suspension of L-tryptophan hydroxamic acid (0.397 g, 1.81 mmol) in 2-propanol (30 mL) was slowly added levulinic acid

(1d) (0.241 mL, 2.35 mmol) at 80 °C. The mixture was stirred at the same temperature and monitored by TLC. After stirring for 2 h at 80 °C, the temperature was raised to 120 °C and toluene (35 mL) was added in small portions in order to remove 2-propanol by azeotropic distillation. After an additional stirring for 7 h, the volatile compounds were evaporated under reduced pressure. To the mixture was added dichloromethane and Na_2CO_3 and stirred vigorously for 1h. The precipitated crystal was filtrated and washed with diethyl ether to give bicyclic hydroxamic acid **3d** (0.516 g, 95%).

(3*S*, 7a*R*)-1-Hydroxy-3-(1*H*-indol-3-ylmethyl)-7a-methyl-dihydro-1*H*-pyrrolo[1, 2-*a*]imidazole-2, 5(3*H*, 6*H*)-dione (3d). Colorless crystal; mp 219-220 °C; R_f 0.34 (ethyl acetate); $[\square]_D^{25}$ +74.7 (c = 1.0, methanol); IR (KBr) 3311, 2658, 1698, 1509, 1459, 1427, 1354, 1136, 751, 595 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) □ 0.65 (s, 3H), 2.07-2.34 (m, 3H), 2.61-2.70 (m, 1H), 3.21-3.37 (m, 2H), 4.52 (t, *J* = 4.9 Hz, 1H), 6.95-7.08 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (68 MHz, CD_3OD) □ 23.5, 27.3, 31.9, 36.0, 59.7, 83.6, 110.8, 112.2, 119.6, 119.8, 122.4, 124.9, 129.6, 137.8, 170.1, 180.8; Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.79; H, 5.73; N, 13.95.

Cyclocondensation of L-phenylalanine hydroxamic acid (1a) with *o*-formylbenzoic acid.

L-Phenylalanine hydroxamic acid (**1a**) (0.360 g, 1.81 mmol), *o*-formylbenzoic acid (0.300 g, 2.00 mmol), *p*-toluenesulfonic acid monohydrate (0.038 g, 0.20 mmol), and benzene (20 mL) were refluxed in a 50 mL two-necked flask equipped with Dean-Stark apparatus for 20 h, after which no more water appeared to be evolved from the reaction. The mixture was concentrated by evaporation until white solid appeared. The solid was filtered off and the filtrate was stood at room temperature. The precipitated white solid was filtered and washed with ether to afford tricyclic hydroxamic acid **9** (0.421 g, 72%). The stereochemistry of **9** was determined by NOE experiments.[20]

(3*S*, 9b*R*)-3-Benzyl-1-hydroxy-1, 9b-dihydro-imidazo[2, 1-*a*]isoindole-2(3*H*), 5-dione (9). Colorless crystal; mp 189-190 °C; R_f 0.51 (ethyl acetate); $[\square]_D^{25}$ +153 (c = 1.0, $CHCl_3$); IR (KBr) 3063, 2924, 2831, 1716, 1695, 1374, 1215, 742, 706, 695, 507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) □ 3.15 (dd, *J* = 5.1, 13.9 Hz, 1H), 3.21 (dd, *J* = 4.1, 13.9 Hz, 1H), 4.59 (t, *J* = 4.4 Hz, 1H), 4.79 (s, 3H), 7.22-7.35 (m, 5H), 7.53-7.63 (m, 3H), 7.81 (d, *J* = 7.2 Hz, 1H), 9.67 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) □ 37.1, 58.8, 74.7, 124.3, 124.8, 127.4, 128.6, 129.9, 130.7, 131.8, 133.2, 135.1, 142.1, 172.5, 173.5; Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.22; H, 4.79; N, 9.48.

Supporting Information: Full experimental detail, ^1H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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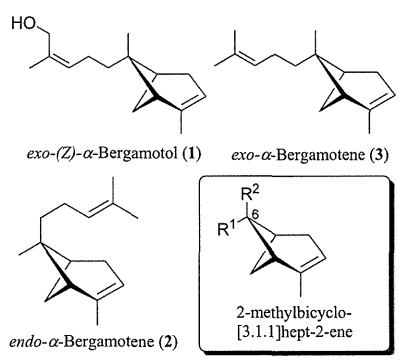
Stereoselective Synthesis of Bicyclo[3.1.1]heptane Derivatives via Intramolecular Photocycloaddition Reaction

Optically active 1,3-bridged cyclobutanes 10 of the bicyclo[3.1.1]heptane ring system and 1,2-bridged cyclobutanes 11 of the bicyclo[3.2.0]heptane ring system were produced by UV irradiation of α,β,γ,δ-unsaturated esters 9a and 9c-f. The preference of *endo*-stereochemistry at C-6 bridged head was observed in *cross*-adducts 10. On the other hand, irradiation of conjugated dienol 9b led via only parallel cycloaddition to 1,2-bridged cyclobutane 11.

Keywords: bicyclo[3.1.1]heptane ring system, photocycloaddition, synthesis of optically active 1,3-bridged cyclobutanes,

East Indian sandalwood oil contains some 4 to 8% of (–)-*exo*-(*Z*)-α-bergamotol ((–)-1), which has bright, somewhat sweet woody fragrance, and is considered to be responsible for the basic sandalwood note [1]. Several synthetic procedures of its representative hydrocarbon counterparts 2 and 3 have been reported. *endo*-α-Bergamotene (2) has been prepared by Gibson and Erman in 12 steps starting from □-pinene [2]. Corey, Cane and Libit have prepared *exo*-α-bergamotene (3) using a photochemical [2+2] cycloaddition of 1,5-diene in 21 steps from geranyl acetate [3]. Larsen and Monti have prepared *endo*-α-bergamotene (2) and *exo*-isomer 3 using intramolecular ring closure for the formation of the cyclobutane ring in 13 steps [4]. Although the direct construction of the acid-labile 2-methylbicyclo[3.1.1]hept-2-ene skeleton and the unambiguous stereocontrol of the quaternary C-6 carbon center have only been partially achieved by these earlier endeavors, these methods do not permit the accumulation of large amounts of material owing to many complicated steps and low overall yields.

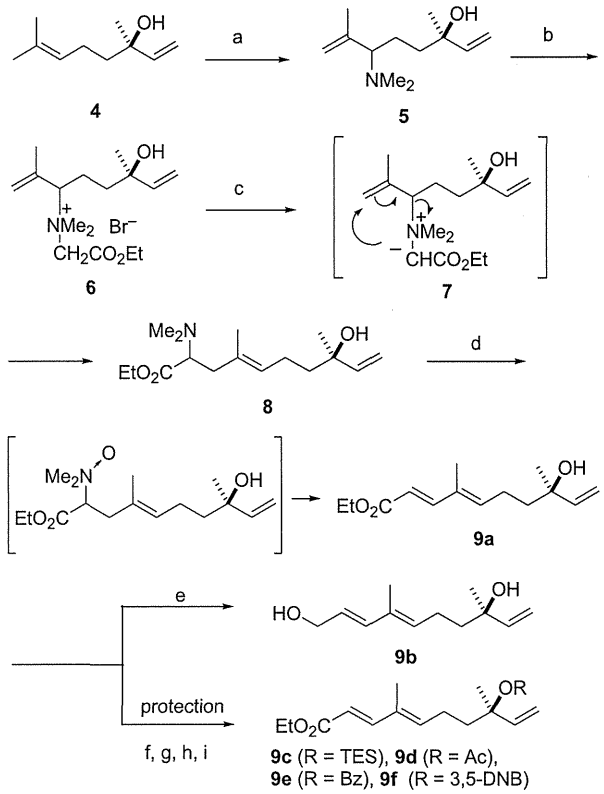


Intramolecular [2+2] photocycloaddition

is an impotant issue in organic synthesis directed towards target molecules. The intramolecular [2+2] photocycloadditions between enone and olefin moieties have been extensively studied in 2-, 3- and 4-substituted alkenylcyclohexenones and found numerous applications in synthesis [5]. To the best of our knowledge, intramolecular [2+2] photocycloaddition of 1,6,8-triene system was hitherto unknown. In this paper we wish to report regiospecific intramolecular [2+2] photocycloadditions of two 1,6,8-trienes *i.e.* α,β,γ,δ-unsaturated ester and conjugated dienol, each of which has a vinyl terminus. Irradiation of β-myrcene resulted in a non-regioselective mixture of several intramolecular products to afford β-pinene in a 22% yield as a result of [2+2] photocycloaddition between two double bonds among the three olefin moieties [6]. Our approach involves the direct construction of the target ring molecule by the irradiation of an acyclic precursor having a distal double bond and an α,β,γ,δ-unsaturated ester moiety which is expected having strong absorption in the ultraviolet region.

We reported an *N*-ylide [2,3]- and [3,3]sigmatropic rearrangement that provides (*Z*)- or (*E*)-trisubstituted olefinic amines with high stereoselectivity [7]. And the [2,3] sigmatropic rearrangement of ammonium ylides having an ethoxycarbonyl group at the □-position afforded exclusively (*E*)-amines [7b]. These amines can be converted to α,β,γ,δ-unsaturated esters via Cope elimination of the corresponding *N*-oxides.

As outlined in Scheme 1, hypochlorous acid, generated in situ from calcium hypochlorite and CO_2, reacted with (*R*)- (–)-linalool (4) to provide allylic chloride, which was treated with dimethylamine in aqueous EtOH at room temperature to give the corresponding allylamine 5 via regioselective S_N2 reaction. Reaction of 5 with ethyl bromoacetate in EtOH provided quaternary ammonium salt 6 in a quantitative yield. Treatment of 6 with NaOEt in EtOH at 0 °C resulted in the formation of ammonium ylide intermediate 7 followed by spontaneous [2,3]sigmatropic rearrangement to give (*E*)-amino ester 8 in 83% yield with 95% stereoselectivity. Furthermore, treatment of 6 with KO*t*-Bu in THF at –70 °C afforded *E*-ester 8 in 72% yield with complete stereoselectivity.

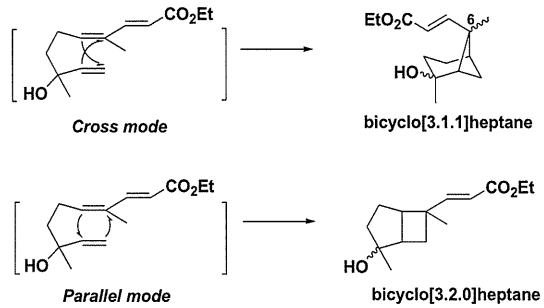


Conditions: (a) (i) $Ca(OCl)_2$, CO_2, CH_2Cl_2, rt, (ii) $HNMe_2$, EtOH, rt, 47% (2 steps), (b) $BrCH_2CO_2Et$, MeOH , rt, quant., (c) KOt-Bu, THF, –70 °C, 72%, (d) AcO_2H, Na_2CO_3 , CH_2Cl_2, –60 °C, 88%, (e) $AlCl_3$ / $LiAlH_4$, ether, 0 °C, 56%, (f) TESOTf, 2,6-lutidine, 84%, (g) AcCl, Et_3N, DMAP, quant., (h)BzCl, DMAP, quant., (i) 3,5-DNBCl, Et_3N, DMAP, 84%.

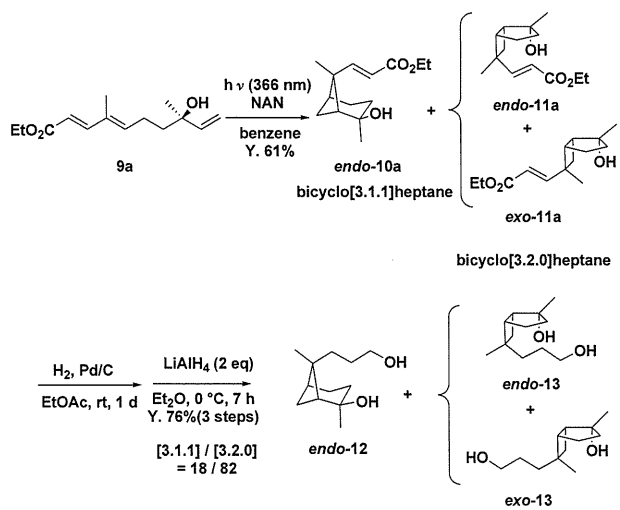
Scheme 1.

Then amino ester 8 was treated with peracetic acid in CH_2Cl_2 at –60 °C in the presence of Na_2CO_3 and the resulting mixture containing the amine oxide was stirred at room temperature for 30 min to give the desired (*E,E*)-α,β,γ,δ-unsaturated ester 9a via Cope elimination of amine oxide in 88% yield with complete stereoselectivity. The ultraviolet absorption spectra analysis showed this unsaturated ester 9a has large ε value (31500) at λ_{max} 267 nm. The subsequent reduction of 9a was most effectively carried out with AlH_3 [8] prepared in situ from $AlCl_3$ and $LiAlH_4$ to give the corresponding unsaturated alcohol 9b in 56% yield. The ultraviolet absorption spectra analysis showed this unsaturated alcohol 9b has large ε value (24700) at λ_{max} 233 nm.

Regioselectivity of cross and / or parallel addition is a crucial point in [2+2] photocycloaddition chemistry. Srinivasan et al. suggested that the initial step, which gives a diradical, involves preferential formation of a five-membered ring ("rule of five") on intramolecular [2+2] photocycloaddition reactions of 1,6-heptadiene [9]. Similar results were obtained on intramolecular [2+2] photocycloaddition
reaction of 3-methylene-1,5-hexadiene system [10].



Irradiation of 9a with the low pressure Hg lamp in each of hexane, c-hexane, diethyl ether or MeOH solution without a photosensitizer gave rise to an unidentified complex mixture of photoadducts. On the other hand, when 9a was irradiated with the high pressure Hg lamp in benzene solution including 5-nitroacenaphthene (NAN) as a photosensitizer, a mixture of cross [2+2] adduct *endo*-10a and parallel photoadducts *endo*-11a and *exo*-11a was formed as a mixture that could not be separated. Then we confirmed these structures strictly by conversion of photoadducts into separable optically active compounds, *endo*-12, *endo*-13 and *exo*-13 [11] as shown in Scheme 2.



Scheme 2.

Thus, hydrogenation followed by reduction with $LiAlH_4$ afforded a cross [2+2] adduct (C-6 stereoisomer) *endo*-12 and a mixture of two parallel photoadducts *endo*-13 and *exo*-13 as separable diols. The accurate ratio of *cross/parallel* was determined by capillary GC analysis. Thus triene 9a gave a 18:82 mixture of two photoadducts which were identified as the cross adduct 10 and the parallel adduct 11 in 61% yield. This interesting result prompted us to investigate [2+2] photocycloaddition of triene 9c-f which was supposed to have an inherent regioselectivity of *cross/parallel*-
addition. Table 1 shows the photocycloaddition results.

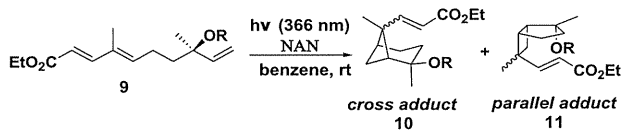


Table 1: Photocycloaddition reaction of triene 9

entry	9	R	Time(h)	Yield(%)	10/11[a]
1	9a	H	2	61	18/82
2	9c	TES	2	52	32/68
3	9d	Ac	3	79	30/70
4	9e	Bz	2	80	41/59
5	9f	3,5-$(NO_2)_2C_6H_3CO$	3	74	25/75

a) The ratio of 10/11 was determined by ^1H NMR and capillary GC analysis after conversion into diols 12 and 13 .

The present photocycloaddition reaction depends on R substituents. When 9c was irradiated in benzene, *cross*-selectivity increased going rise to a 32:68 mixture of two regioisomers, 10c and 11c in 52 % yield (Table 1, entry 2). Interestingly, when 9e was irradiated in benzene solution, the yield of photoadducts 10 and 11 increased up to a 80 % (Table 1, entry 4). In addition, cross-selectivity increased up to 41:59.