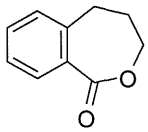


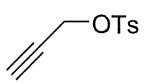
4,5-dihydrobenzo[*c*]oxepin-1(3H)-one (5)

20 mL ナスフラスコに THF(4.65 mL)、化合物 9b (0.427 g, 1.40 mmol)を加え、反応容器を氷浴につけた。フッ化テトラ-n-ブチル

アンモニウム(2.8 mL, 1 mol/L in THF, 2.80 mmol)を滴下し、その後室温で 3 時間撹拌した。酢酸エチルと水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗い、硫酸マグネシウムで乾燥させ、溶媒を減圧留去した。粗生成物はシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1:10)で精製し、目的の化合物 5 を 0.161 g(0.992 mmol, 73%)で得た。

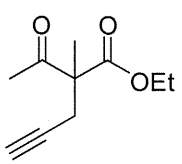
IR (ATR) : 3070, 2861, 1716, 1604, 1468, 1453, 1387, 1356, 1321, 1295, 1279, 1257, 1223, 1199, 1162,1111, 1094, 1058, 1035, 1003, 955 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.09-2.18 (m, 2H), 2.91 (t, J = 7.3 Hz), 4.16 (t, J = 6.3 Hz), 7.21-7.54 (m, 5H)



prop-2-ynyl 4-methylbenzenesulfonate (12)

500 mL ナスフラスコに *p*-トルエンスルホニルクロリド(56.0 g , 294 mmol)、クロロホルム(100 mL)、ピリジン(31.6 ml, 392 mmol)を入れ、0 °C で 10 分間撹拌した後、2-プロピン-1-オール (11.3 mL, 196 mmol)をゆっくり滴下した。7 時間撹拌した後、氷水を加え、ジエチルエーテルで抽出し、有機層を塩酸(1N)、飽和炭酸水素ナトリウム水溶液、飽和食塩水でそれぞれ洗浄した。硫酸マグネシウムで乾燥させた後、溶媒を減圧留去し、粗生成物 **9** を薄黄色のオイルとして得た。



ethyl 2-acetyl-2-methylpent-4-ynoate (13)

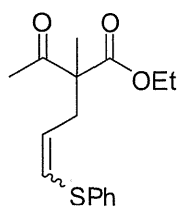
1 L 二口ナスフラスコ中で水素化ナトリウム(14.0 g, 50 % in mineral oil, 294 mmol)をヘキサンで 3 回洗い、THF (500 mL)を加え容器内をアルゴン置換した。0 °C で 2-メチルアセト酢酸エチル(42.0 mL, 294 mmol)を

ゆっくりと滴下し、50°C まで昇温させつつ 1 時間撹拌した後、粗生成物 **12** を滴下して 4 時間撹拌した。溶液を 0 °C に冷却してから飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出し

た。有機層を飽和食塩水で洗い、硫酸マグネシウムで乾燥させた後、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1 : 7)で精製し、化合物 **13** を 25.0 g(137 mmol, 70% for 2 steps)の黄色のオイルとして得た。

IR (ATR) : 3289, 2985, 1713, 1450, 1360, 1238, 1190, 1106, 1019, 858, 652 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.49 (s, 3H), 2.02 (t, *J* = 2.7 Hz, 1H), 2.20 (s, 3H), 2.73 (t, *J* = 3.2 Hz, 2H), 4.21 (dq, *J* = 6.9 and 7.2 Hz, 2H)

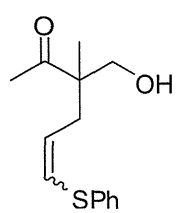


ethyl 2-acetyl-2-methyl-5-(phenylthio)pent-4-enoate (14)

300 mL 二口ナスフラスコに化合物 **13** (5.243 g)、トルエン(100 mL)、2,2'-アゾビス(イソブチロニトリル) (1.62 g, 9.51 mmol)を入れ、アルゴン雰囲気下にした後、ベンゼンチオール(3.40 mL, 31.7 mmol)を滴下した。還流条件下で 2 時間撹拌した後、0 °C に冷却してから 10%水酸化ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗い、硫酸マグネシウムで乾燥させた後、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1 : 6)で精製し、**14** を 7.25 g (24.8 mmol, 86%)の淡黄色のオイルとして得た。

IR (ATR): 2983, 1736, 1711, 1583, 1479, 1440, 1297, 1240, 1184, 1094, 1023, 956, 858, 739, 690 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 1.23 - 1.30 (m, 3H), 1.40 (s, 3H), 2.16 - 2.19 (m, 3H), 2.53 - 2.82 (m, 2H), 4.16 - 4.25 (m, 2H), 5.61 - 5.80 (m, 1H), 6.20 - 6.37 (m, 1H), 7.18 - 7.32 (m, 5H)



3-(hydroxymethyl)-3-methyl-6-(phenylthio)hex-5-en-2-one (15)

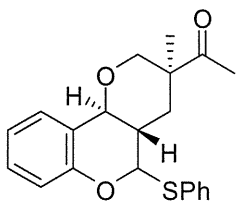
300 mL 二口ナスフラスコに窒素雰囲気下

でジイソプロピルアミン(5.21 mL, 37.2 mmol)、THF (64 mL)を入れ、-78 °C に冷却した後、*n*-BuLi (14.3 mL, 37.2 mmol, 2.6M)を滴下して 0 °C で 30 分撹拌した。-78 °C まで冷却して 30 分間撹拌し、化合物 **14** (7.25 g, 24.8 mmol)を滴下して 3 時間撹拌した。100 mL ナスフラスコにアルゴン雰囲気下で水素化アルミニウムリチウム(1.12 g, 27.3 mmol)に THF (80 mL)を加えたものを先に調整した容器に滴下した後、-40 °C まで昇温して終夜撹拌した。塩酸(1 N)を入れ、ジエチルエーテルで抽

出した。有機層を硫酸マグネシウムで乾燥させた後、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1 : 3)で精製し、**15** を 3.85 g (15.4 mmol, 62%)の淡黄色のオイルとして得た。

IR (neat) : 3460, 2972, 1703, 1583, 1479, 1440, 1357, 1084, 741, 691 cm^{-1}

^1H NMR (270 MHz, $CDCl_3$) : δ 1.22 (s, 3H), 2.22 (S, 3H), 2.40 -2.57 (m, 2H), 3.60 - 3.74 (m, 2H), 5.70 - 5.86 (m, 1H), 6.23 - 6.37 (m, 1H), 7.21 - 7.35 (m, 5H)

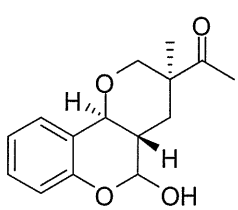


1-((3*S,4a*S**,10b*S**)-3-methyl-5-(phenylthio)-2,3,4,4a,5,10b-hexahydropyrano[3,2-*c*]chromen-3-yl)ethanone (16)**

300 mL 二口ナスフラスコにトルエン (200 mL)、サリチルアルデヒド (2.68 mL, 26.95 mmol)、オルトギ酸トリメチル (1.92 mL, 18.5 mmol)、p-トルエンスルホン酸一水和物 (1.28 g, 7.70 mmol)を加えて室温で 20 分間撹拌した後、化合物 **15** (3.85 g, 15.4 mmol)を加え室温で 3 日間撹拌した。10%水酸化ナトリウム水溶液を加え酢酸エチルで抽出し、有機層を硫酸マグネシウムで乾燥させた後、溶媒を減圧留去した。ジエチルエーテルで固体を析出させ吸引ろ過し、**16** を 2.87 g (8.10 mmol, 53%)の淡黄色の固体として得た。

IR (ATR) : 2983, 2880, 1705, 1609, 1581, 1484, 1458, 1224, 1208, 1078, 1026, 976, 826, 759, 747, 690 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 1.09 (s, 3H), 1.54 (m, 1H), 2.23 (s, 3H), 2.30-2.40 (m, 1H), 2.53 (dt, *J*=3.0, 13.2 Hz, 1H), 3.59 (d, *J* = 12.4 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.56 (dd, *J* = 2.6, 12.2 Hz, 1H), 5.69 (d, *J* = 3.4 Hz, 1H), 6.82-7.01 (m, 4H), 7.17-7.54 (m, 5H)



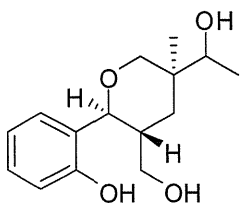
1-((3*S,4a*S**,10b*S**)-5-hydroxy-3-methyl-2,3,4,4a,5,10b-hexahydropyrano[3,2-*c*]chromen-3-yl)ethanone (17)**

1 L ナスフラスコに化合物 **16** (5.48 g, 15.46 mmol)、水 (40 mL)、アセトニトリル (200 mL)を加え 0 °C に冷却した後、アセトニトリル 200mL に溶解した *N*-ブロモスクシンイミド(8.27 g, 46.38 mmol)をゆっくり加え室温で 1 時間撹拌した。溶媒を減圧留去し飽和炭酸水素ナトリウム水溶液を加え、酢酸エチルで抽出し、有機層を硫酸ナトリウムで乾燥させた後、溶媒を減圧留去した。ジ

エチルエーテルで固体を析出させ吸引ろ過し、**17** を 2.60 g (9.90 mmol, 64%)の白色固体として得た。

IR (ATR) : 3340, 1770, 1698, 1609, 1582, 1487, 1457, 1199, 1144, 1063, 974, 749 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 1.06 (s, 3H), 1.48 (t, J = 12.7 Hz, 1H), 1.85 (t, 1H), 2.25 (s, 3H), 2.44 (dt, J = 2.8, 3.0 Hz, 1H), 3.56 (d, J = 12.2 Hz, 1H), 4.46-4.55 (m, 2H), 5.46-5.48 (m, 1H), 6.67-7.51 (m, 4H)

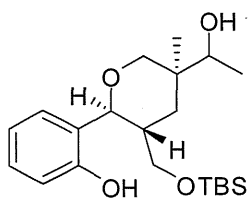


2-((2*S,3*R**,5*S**)-5-(1-hydroxyethyl)-3-(hydroxymethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)phenol (18)**

200 mL ナスフラスコに化合物 **17** (1.23 g, 4.69 mmol)、水素化ホウ素ナトリウム (0.548 g, 14.07 mmol)、メタノール 50 mL を加え、室温で 2 時間撹拌した後、溶媒を減圧留去し 1 規定塩酸を加え、酢酸エチルで抽出し、有機層を飽和食塩水で洗浄した。硫酸ナトリウムで乾燥したのち、溶媒を減圧留去して、粗生成物 **18** を得た。

IR (ATR) : 3342, 2959, 1456, 1245, 1066, 1018, 906, 753 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 0.79 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.39 (t, J = 12.9 Hz, 1H), 2.20-2.27 (m, 1H), 3.37-3.40 (m, 2H), 3.96-4.01 (m, 1H), 4.16-4.20 (m, 1H), 4.38 (d, J = 10.4, 1H), 6.83-7.20 (m, 4H)



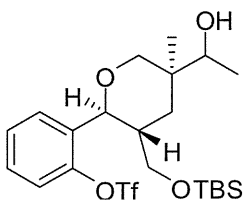
2-((2*S,3*R**,5*S**)-3-((*tert*-butyldimethylsilyloxy)methyl)-5-(1-hydroxyethyl)-5-methyl tetrahydro-2*H*-pyran-2-yl)phenol (19)**

100 mL 二口ナスフラスコに粗化合物 **18** を加え、アルゴン雰囲気下にしたのち、無水ジクロロメタン(25 mL)、トリエチルアミン(1.00 mL, 6.81 mmol)、ジクロロメタンに溶解させた N,N-ジメチル-4-アミノピリジン(0.0.58 g, 0.454 mmol)を加え、反応容器を氷浴に浸した後、*tert*-ブチルジメチルクロロシラン(0.905 g, 5.90 mmol)を加え、室温で 2 時間撹拌した。酢酸エチルと飽和塩化アンモニウム水溶液、水を加え、酢酸エチルで抽出した。有機層を硫酸ナトリウムで乾燥させた

のち、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1:5)で精製し、目的の化合物 **19** を 0.757 g(1.99 mmol, 44% for 2 steps)で得た。

IR (ATR) : 3345, 2954, 2928, 2856, 1586, 1373, 1250, 1069, 903, 833, 776, 752, 667 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 0.004 (d, J = 2.7 Hz, 6H), 0.76 (s, 3H), 0.89 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.22 (t, J = 5.7 Hz, 2H), 2.08 (m, 1H), 3.27 (m, 1H), 3.31-3.35 (m, 2H), 3.93 (dd, J = 9.6 Hz, 1H), 4.13-4.21 (m, 2H), 4.45 (d, J = 11 Hz, 1H), 6.78-7.14 (m, 4H), 7.75 (s, 1H)

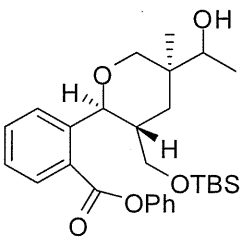


2-((2*S,3*R**,5*S**)-3-((*tert*-butyldimethylsilyloxy)methyl)-5-(1-hydroxyethyl)-5-methyl tetrahydro-2*H*-pyran-2-yl)phenyl trifluoromethanesulfonate (20)**

20 mL ナスフラスコに化合物 **19**(0.190 g, 0.50 mmol)、アセトニトリル(9.0 mL)、ジイソプロピルエチルアミン(0.131 mL, 0.75 mmol)を加え、反応容器を 0℃に冷やしたのち、N-フェニルトリフルオロメタンスルホンイミド(0.273 g, 0.75 mmol)を加えて 0℃で 24 時間撹拌した。溶媒を減圧留去させ、酢酸エチル、水、1 規定塩酸を加え、酢酸エチルで抽出した。有機層を硫酸マグネシウムで乾燥させたのち溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1:5)で精製し、目的の化合物 **20** を 0.123 g(0.240 mmol, 48%)で得た。

IR (ATR): 3450, 2930, 2857, 1725, 1421, 1249, 1209, 1140, 1071, 878, 835, 774, 594 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 0.01 (d, J = 6.0 Hz, 6H), 0.89 (s, 3H), 0.93 (s, 9H), 1.35 (d, J = 6.3 Hz, 3H), 1.39-1.53 (m, 2H), 2.57 (m, 1H), 2.82 (s, 1H), 3.38 (m, 1H), 3.50 (d, J = 12 Hz, 2H), 4.05 (dd, J = 2.7 and 12 Hz, 1H), 4.29-4.36 (m, 2H), 4.64 (d, J = 11 Hz, 1H), 7.37-7.84 (m, 4H)



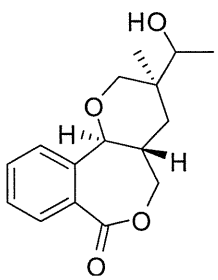
phenyl 2-((2*S,3*R**,5*S**)-3-((*tert*-butyldimethylsilyloxy)methyl)-5-(1-hydroxy ethyl)-5-methyl tetrahydro-2*H*-pyran-2-yl)benzoate (21)**

10 mL ナスフラスコに化合物 **20**(0.174g, 0.339 mmol)、ギ酸フェニル(0.083 g, 0.678 mmol)、トリエチルアミン(0.094 mL, 0.678 mol)を加え、アルゴン雰囲気下にしたのち、無水アセトニ

トリル(1 mL)を加えた混合物を、酢酸パラジウム(0.0067 g, 0.0101 mmol)、ジフェニルホスフィノフェロセン(0.041 g, 0.0288 mmol)を加えアルゴン雰囲気下にしておいた 20 mL 二口ナスフラスコに加え、80℃で 24 時間撹拌した。酢酸エチル、水を加えて、酢酸エチルで抽出した。有機層を飽和食塩水で洗ったのち、硫酸マグネシウムで乾燥させ、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1:5)で精製し、化合物 **21** を 0.106 g(0.219 mmol, 65%)で得た。

IR (ATR): 3457, 2955, 2855, 1735, 1594, 1487, 1386, 1246, 1190, 1160, 1040, 957, 913, 834, 775, 747, 695, 667 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.004 (s, 6H), 0.903 (d, *J* = 2.7 Hz, 9H), 0.86 (s, 3H), 1.25-1.40 (m, 4H), 2.59 (m, 1H), 3.42-3.47 (m, 1H), 3.29 (d, *J* = 12 Hz, 2H), 4.06 (d, *J* = 12 Hz, 1H), 5.21 (d, *J* = 10 Hz, 1H), 7.32-7.86 (m, 8H), 8.21 (td, *J* = 7.5 Hz, 1H)



(3*S,4a*R**11b*S**)-3-(1-hydroxyethyl)-3-methyl-3,4,4a,5-tetrahydro-2*H*-benzo[*c*] pyrano[2,3-*e*] oxepin-7(11b*H*)-one (22)**

20 mL 二口ナスフラスコに化合物 **21**(0.105 g, 0.217 mmol)を入れ、アルゴン雰囲気下にしたのち、無水 THF(1.2 mL)を加え、反応容器を氷浴につけた後、フッ化テトラ-n-ブチルアンモニウム(0.434 mL, 1 mol/L in THF, 0.434 mmol)を滴下し、室温で 24 時間撹拌した。酢酸エチル、水を加えて、酢酸エチルで抽出した。有機層を飽和食塩水で洗ったのち、硫酸マグネシウムで乾燥させ、溶媒を減圧留去した。粗生成物をシリカゲルカラムクロマトグラフィー(AcOEt / hexane = 1:3)で精製し、化合物 **22** を 0.043 g(0.156 mmol, 72%)で得た。

IR (ATR): 3454, 2965, 1723, 1604, 1455, 1385, 1294, 1238, 1126, 1077, 1036, 911, 799, 764, 711, 671, 620 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.827 (d, *J* = 8.4 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.70 (t, *J* = 13 Hz, 2H), 1.94-1.99 (m, 1H), 3.25 (d, *J* = 12 Hz, 1H), 3.92-4.24 (m, 3H), 4.35-4.42 (m, 2H), 7.37-7.74 (m, 4H)

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G．研究発表

1. 論文発表

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.

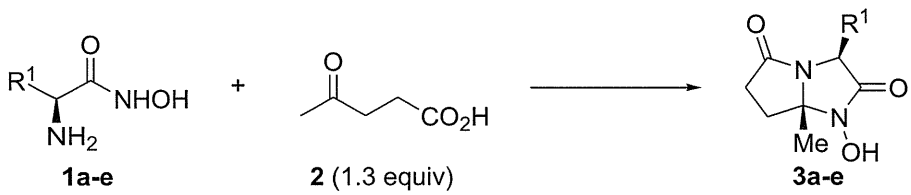
Chiral acyclic hydroxamic acids have recently received increasing attention as a chiral ligand in the field of asymmetric transition-metal catalysis such as epoxidation of alkenols[11]

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).

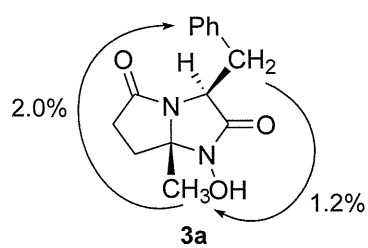


1a-e **2** (1.3 equiv) **3a-e**

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

Table 1. Cyclocondensation of · -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



3a

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

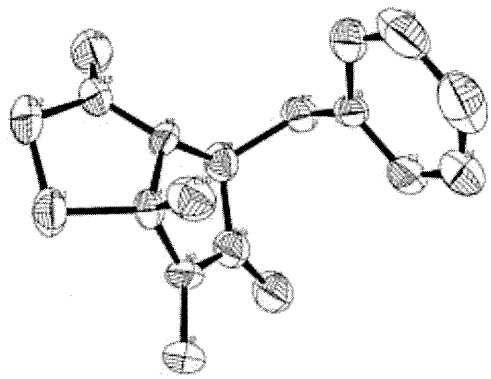
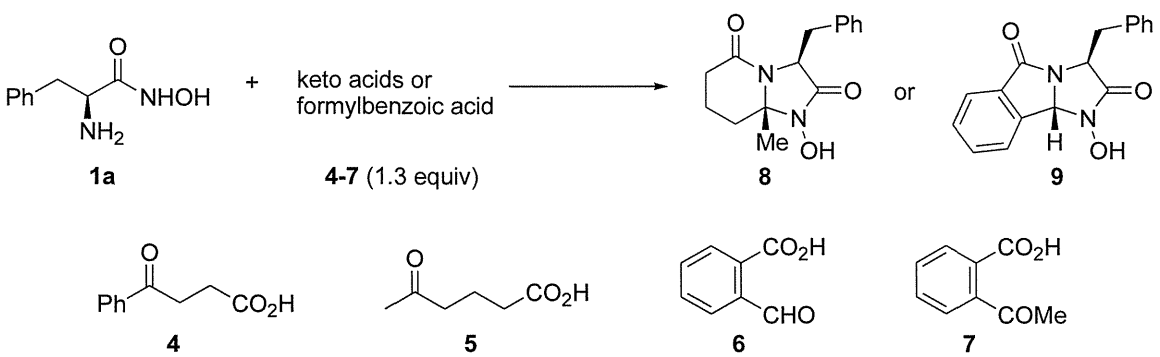


Figure 2. ORTEP diagram of **3a**.

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.

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); $[\cdot]_D^{25}$ +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); $[\cdot]_D^{25}$ +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); [·]$_D^{25}$ +153 (c = 1.0, $CHCl_3$); IR (KBr) 3063, 2924, 2831, 1716, 1695, 1374, 1215, 742, 706, 695, 507 cm^{-1}; ^{1}H 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, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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1,2-oxazinane　dihydro-1,2-oxazine

2. 学会発表

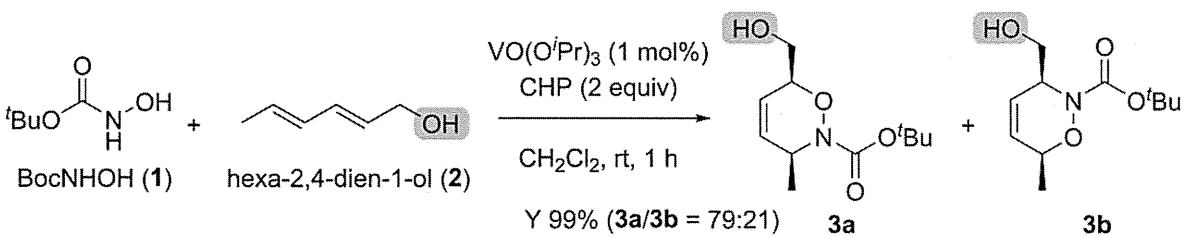
2.1. 星野雄二郎、新保雄基・鈴木健三・本田 清、第 57 回　香料・テルペンおよび精油化学に関する討論会、埼玉、2013.10.5-6.

ニトロソカルボニル Diels-Alder 反応を用いた官能性 1,2-オキサジンの合成

1. はじめに

1,2-オキサジナンは、官能基化された□□□-アミノアルコールやピロリジンなどの有用合成中間体として有望であり、また、生理活性化合物の一部としてしばしば見られる骨格でもあり、官能基化された 1,2-オキサジナンやその不飽和体のジヒドロ-1,2-オキサジンの効率的合成法の開発が望まれる。ニトロソカルボニル化合物は Diels-Alder 反応において良好な親ジエン体として働き、ジヒドロ-1,2-オキサジンを与えることが知られている [1]。しかし、単離が困難なため系中で発生させて反応を行う必要がある。代表的従来法としては、一旦 Diels-Alder 付加体を合成し、それを加熱して逆 Diels-Alder 反応によりニトロソカルボニル化合物を発生させる方法と、ヒドロキサム酸を過ヨウ素酸塩によって酸化して得る方法の二種類が知られている。これらの方法では多段階や、大量の副生成物を発生するといった問題点が指摘されている。グリーンケミストリーの観点から、触媒を用いる環境にやさしい酸化反応系の構築が望まれており、過酸化物を酸化剤とする金属触媒を用いたヒドロキサム酸の酸化が、ニトロソカルボニル化合物を発生させる有望な方法として近年注目を集めている [2]。

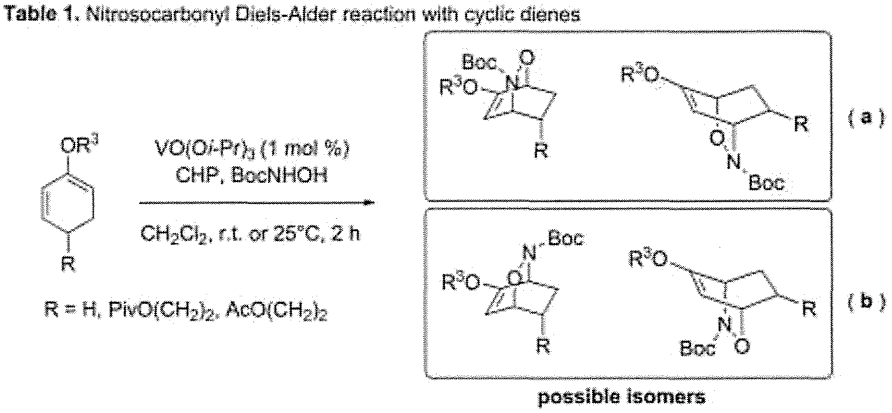
我々は酸素との親和力が高い前周期遷移金属に着目し、バナジウム錯体を触媒とした *N*-ヒドロキシカルバミン酸誘導体の酸化反応を検討したところ、室温で高選択的に酸化反応が進行し、速やかにニトロソ化合物が発生することを見出した（**Scheme 1**）[3]。アルコール官能基が存在しても

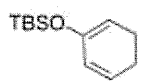
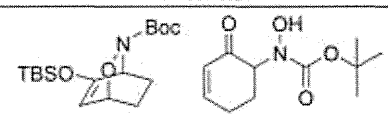
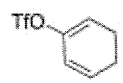
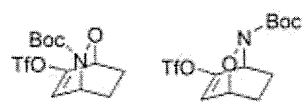
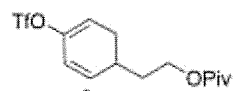
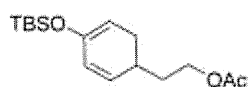
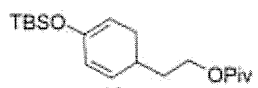


BocNHOH (**1**)　hexa-2,4-dien-1-ol (**2**)

Scheme 1. Vanadium-catalyzed oxidation of N-hydroxycarbamate.
CHP: cumene hydroperoxide

Table 1. Nitrosocarbonyl Diels-Alder reaction with cyclic dienes



Entry	Reactant	Products	Yield (%)
1 [a]	 4	 5b 6	**5b:** 13 **6:** 24
2	 7	 8a 8b	**8a:** 16 **8b:** trace
3	 9	**10a, 10b**	**10a:** 67 (37 : 30) **10b:** 13
4	 11	**12b**	**12b:** 60 (37 : 23)
5	 13	**14a, 14b**	**14a:** 11 **14b:** 29 (17 : 12)

高い選択性でヒドロキサム酸を酸化し、アルデヒドなどの副生成物は全く見られないことが大きな特色であり、官能基化されたジヒドロ-1,2-オキサジン合成法として期待がもたれる。今回我々は天然物合成などに応用できる、環状ジエンとのニトロソカルボニル Diels-Alder 反応を検討したので、それらの結果について報告する。

2. 結果および考察

まず、無置換のシクロヘキセノンから誘導されるジエン **4** と **7** を用いてニトロソカルボニル Diels-Alder 反応を検討した（**Table 1**）。シリロキシ基が置換したジエン **4** からの付加体は比較的不安定であり、カラムクロマトグラフィーにより単離したところ付加体 **5b** が収率 13%で得られた。その付加体の分解生成物と思われるヒドロキシアミノケトン **6** も得られてきたことから、後