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Levopimaric acid derived 1,2-diamines and their application in the copper-catalyzed asymmetric Henry reaction

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ABSTRACT

Levopimaric acid, a readily available starting material, was used in efficient syntheses of new enantiopure diamines and Schiff bases with good yields. The synthetic procedure is based on the fumaropimaric acid monomethyl ester conversion into the optically pure *trans*-1,2-diamine via a Curtius rearrangement. New diamines were studied as ligands in the copper-catalyzed asymmetric Henry reaction.

1. Introduction

Natural products are a convenient and promising source of renewable raw materials for organic synthesis. Chiral natural compounds are widely used in drug discovery, asymmetric synthesis, and enantiomers separation. Metal complexes with chiral ligands based on amino acids, terpenes, carbohydrates, alkaloids have been applied as catalysts for enantioselective reactions.[1–4] Starting from natural monoterpenes a large variety of its nitrogen derivatives (diamines, amino alcohols, Schiff bases, imidazolines) have been synthesized and employed as chiral inducers in asymmetric catalysis.[5–11] The application of diterpenes for this purpose is much less studied. Among the few examples known, dehydroabietylamine and isosteviol were used as chiral moieties incorporated into organocatalysts.[12–16] Diterpene resin acids are a promising chiral source for the construction of various optically active substances as they are commercially available optically pure reactive compounds possessing multiple stereogenic centers and modifiable functional groups.

Earlier, we developed methods for the synthesis of optically pure nitrogen and phosphorus derivatives of diterpene resin acids and employed the resultant mono- and bidentate N, P-ligands in catalytic asymmetric reactions.[17,18] Here we present a high yield procedure for an optically pure diterpene derived *trans*-1,2-diamine and its further use as a key compound for obtaining a series of secondary amines with different substituents. These novel diamine ligands were employed in the Cu(II)-catalyzed Henry reaction. The asymmetric nitroaldol reaction (Henry reaction) is an important method in organic synthesis, used for the creation of C–C bonds via condensation of carbonyl compounds with saturated nitroalkanes.[19–22] The Henry reaction is efficiently catalyzed by complexes of copper(I) and copper(II) with nitrogen containing ligands, including oxazoline (bisoxazoline),[23–27] amines,[28–31] amine oxides,[32] aminoalcohols,[33–36] sulfonylamides,[37] Schiff bases[38] and salans.[39–43] Most of the chiral amine ligands used contain *trans*-diamine fragments from 1,2-diaminocyclehexane[29,42–47] or 1,2-diphenylethanediamine.[39,41,48,49] The essential advantage of the Cu(II) complexes over those of Cu(I) is that they do not require inert atmosphere for catalysis performance.[32,50,51] With this regard herein we report the employment of a new *trans*-1,2-diamine scaffold type in chiral Cu(II) complex catalysts for nitroaldol condensation.

2. Results and discussion

2.1. Synthesis of 1,2-diamine derivatives of levopimaric acid

After considering the properties of levopimaric acid **1** and the other constituents in the starting plant feedstock[52,53] we designed an

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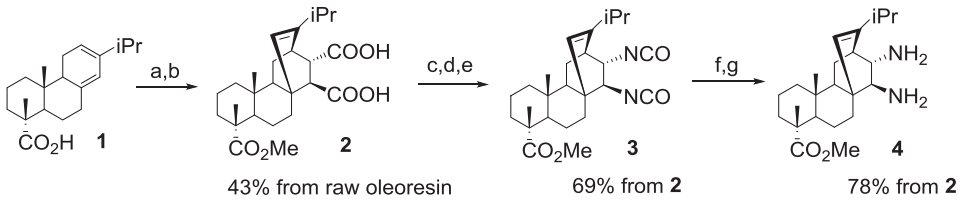


Scheme 1. Synthesis of diamine **4** from pine oleoresin, containing levopimaric acid **1**. Reagents and conditions: (a) CH_3I, K_2CO_3, acetone, 6 h; (b) fumaric acid, 180 °C, Ar, 6 h; (c) $SOCl_2$, DMF, 110 °C, 3 h; (d) NaN_3, $PhCH_3$, +5 °C, 2 h; (e) 110 °C, 2 h; (f) HCl (35%), 110 °C, 2 h; (g) aqueous $NaHCO_3$.

optimum sequence for the synthesis of the 1,2-diamine (Scheme 1). Pine oleoresin is mainly composed (75–95%) of mixed abietic-type resin acids,[54–59] i.e. tricyclic diterpenes with a single carboxyl group and a conjugated double bond system. The four abietic-type acids (abietic, neoabietic, palustric and levopimaric) undergo interconversion under heat or acidic conditions,[60–62] and in the fresh pine resin levopimaric acid **1** amounts to 30–50%.[52,61] Owing to its *cis*-diene structure, levopimaric acid easily reacts with activated dienophiles at 20–30 °C forming the Diels-Alder adducts.[52,63] Other abietic-type acids form the same adducts at 150 °C after *in situ* isomerization into levopimaric acid.[63–66] Cycloaddition proceeds with a high stereoselectivity[66] and the target product is easily separated by crystallization from both minor isomers and non-reacted feedstock components due to a difference in the solubility of the diastereoisomers. The obtained optically pure cycloaddition adduct **2** contains *trans*-1,2-carboxyl groups, which can be used to introduce amino groups through Curtius rearrangement.

The raw pine oleoresin with high content of abietic-type acids was used as the starting material for the synthesis of 1,2-diamine **4** without any purification or isolation of the resin acids. In order to avoid undesired triamine formation the oleoresin was methylated before the diene synthesis. Cycloaddition of fumaric acid to the methyl levopimarate was performed without a solvent at 180 °C under argon using the crude mixture of the methylated products obtained at the previous stage. Unreacted oleoresin components were removed from the resultant reaction mixture by extraction with diethyl ether. The residual crude solid was crystallized from methanol yielding individual product **2** at 50 g per 100 g of the raw oleoresin used. The obtained monomethyl ester of fumaropimaric acid **2** is stereochemically pure, which is confirmed by the single set of signals in ^1H and ^{13}C NMR spectra.

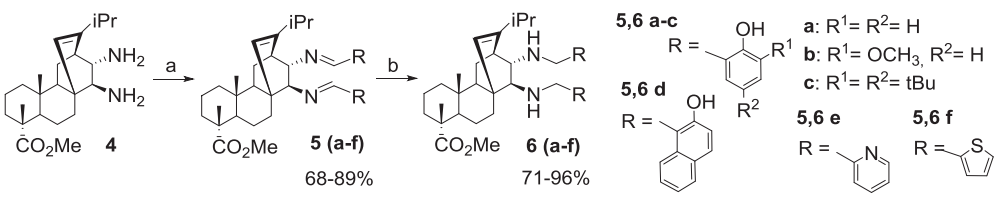
The four stage conversion of monomethyl ester of fumaropimaric acid **2** into *trans*-1,2-diamine **4** via Curtius rearrangement was performed as a one pot procedure without any separation of intermediates (acid dichloride, diazide and diisocyanate). The overall yield was 78%. Intermediate diisocyanate **3** was also synthesized from dicarboxylic acid **2** and isolated in a yield of 69%. Synthesis of the target diamine **4** proceeds stereospecifically, giving an optically pure product which is then used to obtain chiral Schiff bases and secondary amines (Scheme 2).

New Schiff bases **5a-f** were obtained in good yields (68–89%) via *trans*-1,2-diamine **4** condensation with several aromatic aldehydes. Reduction of compounds **5a-f** by sodium borohydride afforded amines **6a-f** isolated in yields of 71–96% after chromatography or crystallization. Therefore, we have synthesized new levopimaric acid derived optically pure secondary amines **6a-f** containing various substituents at the nitrogen atoms.

2.2. New chiral diterpene derived 1,2-diamine ligands in enantioselective Cu(II)-catalyzed Henry reaction

The enantioselectivity and catalytic activity of Cu(II) complexes with ligands **6a-f** were estimated in nitroaldol reactions using 4-nitrobenzaldehyde **7a** and nitromethane **8** as model substrates. Reactions were carried out in tetrahydrofuran solution at room temperature in the presence of a 5 mol% *in situ* catalyst prepared from copper(II) acetate monohydrate (5 mol%) and ligands **6a-f** (5 mol%) just before the Henry reaction. The results of the reactions are shown in Table 1. High chemical and moderate % ees were obtained in nitroaldol condensation in the presence of copper complexes with aminophenols (Table 1, entries 1–2) and aminonaphthol (Table 1, entry 4). As the substituent at the *o*-position of ligand phenol ring increases in volume, the reaction rate and % ee decrease (Table 1, entries 1–3). At the same time, volume of substituents at *m*- or *p*-positions have a lesser effect on catalyst performance (Table 1, entry 4). Obviously, the presence of phenol donor oxygen atoms in the non-chiral substituents at ligand amino groups is necessary for catalyst enantioselectivity. Thus, when the phenol substituents are replaced by heterocyclic ones, the derived metal complexes show moderate or high catalytic activity but negligible stereodifferentiating ability (Table 1, entries 5, 6). Therefore, in further experiments we studied catalyst performance of copper(II) complex with only chiral ligand **6a**.

The results of model reactions carried out in different solvents are shown in Table S1 (see Supporting Information). Since the precursors and catalyst itself well dissolve in all tested solvents, the solvent polarity and specific interactions with metal complex appear to be the main factors determining catalyst efficiency. Reactions in non-polar solvents (Table S1, entries 1–2) afforded product in moderate yields (53–63%) with low *ee* (24%). Similar results are also obtained in chlorinated hydrocarbons (Table S1, entries 3–4). Protic solvent MeOH (Table S1, entry 5) decreases the enantioselectivity even more (to 15% *ee*) most likely due to alcohol coordination to copper providing a mixture of metal complexes. In acetonitrile and dimethylformamide (Table S1, entries 6, 7) nitroaldol condensation resulted in high yield, but near racemic products are attained. Apparently, copper(II) forms non-chiral complexes with these solvents, which hinder formation of



Scheme 2. Synthesis of levopimaric acid derived Schiff bases and diamines. Reagents and conditions: (a) RCHO; (b) $NaBH_4$.

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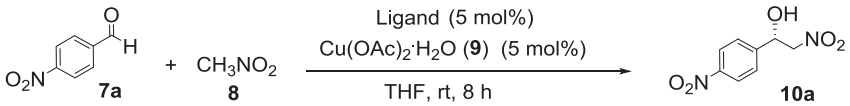
Table 1
Screening of Cu(II) complexes with ligands **6a-f**.[a]



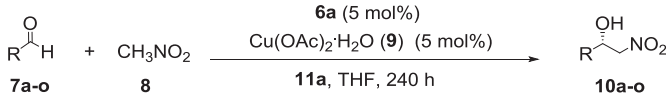
Entry	Ligand				Yield (%)[b]	*ee* (%)[c]
		R (Scheme 2)	R^1	R^2		
1	**6a**	2-OH,3-R^1,4-R^2-C_6H_2	H	H	98	40
2	**6b**	2-OH,3-R^1,4-R^2-C_6H_2	OCH_3	H	85	33
3	**6c**	2-OH,3-R^1,4-R^2-C_6H_2	Bu^t	Bu^t	33	10
4	**6d**	2-hydroxynaphthyl	–	–	88	35
5	**6e**	2-pyridyl	–	–	98	0
6	**6f**	2-tiophenyl	–	–	60	5

[a] All reactions were carried out using [**7a**] = 0.2 M, [**8**] = 2.0 M, [**9**] = 0.01 M (5 mol%), [**6a-f**] = 0.01 M (5 mol%), in THF (2 mL) at rt for 8 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC on the chiral phase.

stereodiscriminating complex with the chiral ligand.[67] An improvement in enantioselectivity was achieved in tetrahydrofuran, which appears to be the optimum solvent for the reaction providing the product **10a** in the highest yield (99%) and with 40% *ee* (Table S1, entries 8–11). Under these conditions, higher ligand/metal ratio had no effect on the catalyst's performance (Table S1, entries 10–11). Lowering reaction temperature to −5 °C provides an enantioselectivity increase to 48% *ee* beside the expected decrease in reaction rate (Table S1, entry 9).

In some Henry reactions the rate is known to increase in the presence of a combined catalytic system including an external base, additionally activating nitromethane. The use of the base in optimum concentration can also increase enantioselectivity.[68] We have investigated the effect of various amines addition on the outcome of the reaction in the presence of the copper(II) complex with ligand **6a** (see Table S2 in the Supporting Information, entries 4–8). It was found out that at −5 °C none of tested external bases (10 mol %) had a significant effect on the reaction's enantioselectivity

Table 2
Scope of aldehydes.[a]



Entry	RCHO	R	Product	**11a** (mol%)	*T* (°C)	Yield (%)[b]	*ee* (%) (*S*)[c]
1	**7a**	4-$NO_2C_6H_4$	**10a**	–	−5	98	48
2	**7a**	4-$NO_2C_6H_4$	**10a**	100	−5	98	65
3	**7a**	4-$NO_2C_6H_4$	**10a**	–	−25	98	66
4	**7a**	4-$NO_2C_6H_4$	**10a**	100	−25	95	78
5	**7b**	2-$NO_2C_6H_4$	**10b**	–	−5	98	54
6	**7b**	2-$NO_2C_6H_4$	**10b**	100	−5	98	72
7	**7b**	2-$NO_2C_6H_4$	**10b**	–	−25	98	65
8	**7b**	2-$NO_2C_6H_4$	**10b**	100	−25	83	82
9	**7c**	3-$NO_2C_6H_4$	**10c**	100	−25	88	81
10	**7d**	2-ClC_6H_4	**10d**	–	−5	75	56
11	**7e**	3-ClC_6H_4	**10e**	–	−5	82	58
12	**7f**	4-ClC_6H_4	**10f**	–	−5	82	56
13	**7g**	2-MeC_6H_4	**10g**	–	−5	63	70
14	**7g**	2-MeC_6H_4	**10g**	100	−5	35	75
15	**7g**	2-MeC_6H_4	**10g**	–	−25	20	79
16	**7g**	2-MeC_6H_4	**10g**	100	−25	11	81
17	**7h**	3-MeC_6H_4	**10h**	–	−5	79	52
18	**7i**	4-MeC_6H_4	**10i**	–	−5	80	46
19	**7i**	4-MeC_6H_4	**10i**	100	−5	41	55
20	**7i**	4-MeC_6H_4	**10i**	–	−25	18	57
21	**7i**	4-MeC_6H_4	**10i**	100	−25	15	69
22	**7j**	4-$MeOC_6H_4$	**10j**	–	−5	72	51
23	**7k**	3,4-$(MeO)_2C_6H_3$	**10k**	–	−5	68	46
24	**7l**	2-thienyl	**10l**	–	−5	84	40(*R*)[d]
25	**7m**	Ph	**10m**	–	−5	65	48
26	**7n**	iPr	**10n**	–	−5	6	25
27	**7o**	Cy	**10o**	–	−5	7	18

[a] All reactions were carried out using [**7a-m**] = 0.2 M, [**8**] = 2.0 M, [**9**] = 0.01 M (5 mol%), [**6a**] = 0.01 M (5 mol%) in 2 mL of THF for 240 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC on the chiral phase.
[d] Formal inversion of the stereodescriptor due to the Cahn–Ingold–Prelog (CIP) notation.

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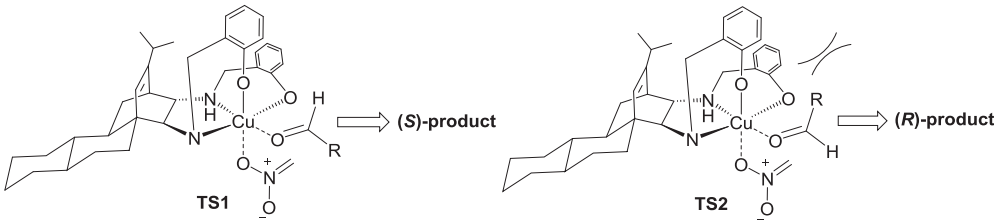

Fig. 1. Proposed transition state models for the copper-catalyzed enantioselective Henry reaction with ligand **6a**.

(Table S2, entries 4, 5, 8). At reaction temperatures of −25 °C, the *ee* increased (from 48 to 66%), but the reaction rate decreases dramatically (Table S2, entry 1). Under these conditions 10 mol% of triethylamine added to substrate increases reaction rate with no loss in enantioselectivity (Table S2, entry 6). As the triethylamine amount is increased to 100 mol %, the reaction rate increases even more, but enantioselectivity decreases (Table S2, entries 2 *vs* 7). It should be noted that water presence in reaction mixture has no effect on both catalyst activity and enantioselectivity (Table S2, entry 3).

We also studied the effect of phenols additives on the nitroaldol reaction (Table S2, entries 8–17). Positive effect of phenols as achiral additives on product yields and enantioselectivities for organocatalytic Henry reaction is reported elsewhere.[69] In our Cu(II)-catalyzed case, 3-nitrophenol addition also appears to increase the enantioselectivity of nitroaldol condensation (Table S2, entries 12–16). As the phenol additive concentration increases, *ee* values grow slightly (at −5 °C: from 55% at 10 mol% of 3-nitrophenol to 65% at 100 mol%). At the same time, other studied phenols, including isomeric 2- and 4-nitrophenols, have no effect on reaction outcome. Lowering the temperature to −25 °C with addition of equimolar amount of 3-nitrophenol to substrate improves the enantioselectivity to 78%. However, reaction slows down considerably giving the addition product **10a** in a yield of 32% (Table S2, entry 16). A simultaneous addition of triethylamine and 3-nitrophenol (Table S2, entry 17) in equimolar amounts (100 mol %) at −25 °C provides the same product yield (94%) as obtained at solely triethylamine addition in concentration of 100 mol% (Table S2, entry 7) with the lower *ee* (28%). Both triethylamine and 3-nitrophenol additives have effect on the reaction rate and selectivity, but not on the product configuration. In all experiments nitro alcohols with an (*S*)-configuration were produced.

To assess the contribution of components to the catalytic system $Cu(OAc)_2$/ligand **6a**/3-nitrophenol performance, we carried out experiments at room temperature using each of them separately as a catalyst. According to Table S3 (see Supporting Information) in the absence of copper(II) aminophenol **6a** does not catalyze Henry reaction with (Table S3, entry 3) or without (Table S3, entry 1) 3-nitrophenol. Solely 3-nitrophenol also shows no catalytic performance in this reaction (Table S3, entry 2). In all cases, the reaction proceeds with no selectivity and nitro alcohol **10a** yield never exceeds 3% over 18 h. On its own $Cu(OAc)_2$ shows weak catalytic activity and no enantioselectivity (Table S3, entry 4). Only Cu(II) precursor with ligand **6a** shows high catalytic activity and moderate enantioselectivity (Table S3, entry 5).

Based on these results, we assume that the 3-nitrophenol does not directly bind to the stereodiscriminating catalytic copper complex. The reaction deceleration and improvement of enantioselectivity caused by 3-nitrophenol addition can be attributed to the formation of its molecular complex with benzaldehyde (similar to ones described elsewhere[70]), which hinders aldehyde coordination, but provides the better control over its orientation when approaching to the Cu complex.

Investigation of the reagent concentrations and substrate/catalyst ratio showed that a decrease in the value of both these parameters led to lower yields and selectivities, while their increase had an insignificant effect on reaction outcome (Table S3, entries 6–10). Based on the above results, the optimal reaction conditions are: ([**7a**] 0.2 M, [**8**] 2.0 M, [**9**] 0.01 M (5 mol%), [**6a**] 0.01 M (5 mol%), [**11a**] 0.2 M).

Having established the conditions affecting the reaction yield and enantioselectivity, we investigated the effects of substituents on the aromatic ring of the aldehydes on the outcome of the nitroaldol reaction (Table 2). The reactions were studied at −5 °C and −25 °C, both with and without 3-nitrophenol depending on the reactivity of the aldehydes. Product yields and *ee* values were examined after 10 days of the reaction, when advanced substrate conversion was noticeable in all experiments. As can be seen from the Table 2, nitroaldol condensation rate and enantioselectivity depend on both electronic and steric effects of substituent on the aldehyde aromatic ring. It was also revealed that all tested aldehydes formed Henry adducts with (*S*)-configuration of major enantiomer.

A higher electronegativity of substituent facilitate aldehyde activation and thus increases reaction rate. The highest yields (83–98%) were obtained with nitro-substituted benzaldehydes (Table 2, entries 1–9). Conversely, electron-donating substituents deactivate aromatic aldehyde and the condensation slows (Table 2, entries 13–23). Lowering the temperature and 3-nitrophenol addition further reduce yields to 11–35% (Table 2, entries 13–16), but improve the *ee*. According to this correlation, chlorinated benzaldehydes should be more activated reagents than tolyl aldehydes and less activated than nitro substituted ones. Reaction of chlorobenzaldehydes afforded products in 75–82% yields (Table 2, entries 10–12). Steric factors also affect the reaction rate. The closer that a substituent is to the formyl group in aromatic ring, the slower the condensation is (Table 2, entries 4, 8, 9, and 10–12, and 13, 17, 18). This effect is more pronounced for the larger volume substituents. The reaction's enantioselectivity is more dependent on the steric effect of the substituent in the aldehyde then on its electronic properties. The highest *ee* are obtained for benzaldehydes with bulky nitro (Table 2, 54–82% *ee*) and methyl (Table 2, 70–81% *ee*) substituents at the *o*-position (Table 2, entries 5–8, 13–16). Variation of the distance from the formyl group to the smaller substituent (chlorine atom) has no effect on the enantioselectivity (Table 2, entries 10–12). In all cases temperature lowering and 3-nitrophenol addition decrease chemical yields but increase *ee* values, i.e. the reaction decelerating factors improve enantioselectivity. Under the same conditions, two aliphatic aldehydes were tested and provided the corresponding products with low yields and enantioselectivities (Table 2, entries 26–27).

Based on our experimental observations and the previously reported steric and electronic considerations[23,28,39] we propose the transition state models for the enantioselective Henry reaction (Fig. 1). Two neighboring strong coordination sites at the equatorial positions of the Cu complex are occupied by the 1,2-nitrogen atoms

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of the ligand. Phenol oxygen atoms of the ligand coordinate to the equatorial and apical positions. For maximum activation of both the reagents in the transition state, the aldehyde carbonyl group should bind to metal center in the equatorial position, while the oxygen atom of nitromethane is positioned perpendicular to the ligand plane. The aldehyde molecule coordinates to the copper ion with the bulky R group oriented towards the less-crowded space as a result of the steric hindrance from the upward oriented phenyl moiety of the ligand. This implies that attack of the nitronate would take place preliminary to *Re* face of the carbonyl group (**TS1**) to give *S* isomer as the major product.

3. Conclusion

Therefore, we have developed a new convenient and easily reproducible synthetic route for the diamine functionalization of abundant resin acids applicable as building blocks with a non-conventional scaffold. Synthesis of the new enantiomerically pure vicinal *trans*-diamines and Schiff bases have been performed in few steps with good to high yields from a commercially available plant feedstock – oleoresin with high abietic-type acids content. Efficient and scalable synthesis protocols using readily available starting materials open up possibilities of broad application of the diterpene diamines in asymmetric synthesis. These enantiopure products can serve as useful intermediates for the construction of more complex chiral molecules: bioactive compounds, resolving agents, auxiliaries and chiral catalysts. The new secondary diamines **6** were tested as chiral ligands for the copper (II)-catalyzed asymmetric nitroaldol reaction of nitromethane with substituted aromatic aldehydes, giving enantioenriched nitroalcohols with up to 98% yields and up to 82% ee. This is the first example of diterpene based chiral 1,2-diamine application in asymmetric catalysis and the best result for the for the catalyst with the source of chirality composed only by diterpene unit. Studies aimed at modifications of these ligands as well as applications to other asymmetric reactions are currently ongoing in our laboratory.

4. Experimental section

4.1. General information

The chemicals were of reagent purity grade, obtained from commercial sources, and used without further purification. Pine oleoresin OST 13-128-93 (Russian industry standard; oleoresin contains at least 80% of abietic-type acids) was obtained from Orgsyntez OJSC (available on request at http://orgsyntez.ru/en) and used as received. Solvents were distilled from appropriate drying agents prior to use, unless otherwise noted. Flash column chromatography was performed on silica gel (Panreac 40–63 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-500, AM-400 and AV-300 spectrometers. Chemical shifts were reported in the δ scale using the residual solvent peak of the $CHCl_3$ as a reference (7.26 ppm) for ^{1}H NMR spectra and the middle signal in the triplet of $CDCl_3$ (77.00 ppm) for ^{13}C NMR samples. Optical rotations were measured on a polAAr 3005 instrument with a 100 mm cell (concentration **c** in g/100 mL). HRMS experiments were performed on DFS spectrometer. IR spectra were recorded using Infralum FT-801 or Shimadzu IRAffinity-1 FT-IR spectrometers. Elemental analyses (CHN) were performed on a EURO EA 3000 Elemental Analyzer. HPLC analyses were performed on Varian ProStar instrument with a ProStar 335 Photodiode Array Detector and with chiral column Chiralcel OD-H. GC-MS analysis of methyl esters of resin acids was carried out on SHIMADZU GCMS-QP2010 Ultra instrument on the basis of gas chromatograph GC-2010 plus with mass detector and with chromatographic column GsBP1-MS 30 m × 0.32 mm.

Chromatogram of methylated oleoresin and copies of spectra of fumaropimaric acid derivatives **2**–**6** see in Ref. 71 (Figs. 1, S2–S6).

4.2. Synthesis of fumaropimaric acid derivatives

4.2.1. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-dicarboxy-4-carboxylic acid methyl ester *2*

Anhydrous potassium carbonate (55 g, 0.4 mol) and methyl iodide (22 mL, 0.35 mol) were added to the solution of raw pine oleoresin (100 g, 0.27 mol of abietic-type acids) in acetone (800 mL). The reaction mixture was refluxed for 5 h, then cooled to room temperature and solid was filtered. The filtrate was concentrated under reduced pressure, the residue was dissolved in diethyl ether (300 mL), insoluble solid was filtered, and the resulted solution was evaporated under reduced pressure. The residue was analyzed by GC-MS (see Ref. 71, Fig. 1). To the residue, fumaric acid (55 g, 0.47 mol) was added and the reaction mixture was heated at 180–200 °C under stirring and an argon atmosphere for 6 h. Then the reaction mixture was cooled to room temperature and diethyl ether (300 mL) was added. The resulting precipitate was filtered, washed with hot (90 °C) water (4 × 400 mL) and dried on air. The crude product was crystallized from methanol to give the pure diacid **2** as colourless cubic crystals; yield 50 g (43%). Characterization data for **2** are consistent with values previously reported.[18]

4.2.2. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-diamino-4-carboxylic acid methyl ester *4*

Neat DMF (0.2 mL, 2.6 mmol) and thionyl chloride (8.4 mL, 116 mmol) were added to the stirred suspension of **2** (20 g, 46 mmol) in toluene (80 mL). The reaction mixture was refluxed until complete dissolution of **2**. A part of the toluene (15 mL) and the residual thionyl chloride were removed under reduced pressure. The resultant toluene solution was cooled (10–15 °C) and added dropwise over 10 min to a vigorously stirred and cooled (0–5 °C) solution of sodium azide (CARE! Toxic! Explosive!) (12 g, 185 mmol) and Aliquat 336 (0.5 g, 1.2 mmol) in water (100 mL). The reaction mixture was stirred for 2 h at 0–5 °C. The organic layer was separated and the aqueous phase was extracted with toluene (2 × 30 mL). The combined organic layers were washed with saturated solution of sodium chloride (1 × 30 mL) and dried over Na_2SO_4. The resulting toluene solution was slowly heated with a long reflux condenser (40 cm) (ATTENTION! The reaction is highly exothermic!) and refluxed until the nitrogen evolution has stopped. Then the reaction mixture was cooled to the room temperature and concentrated hydrochloric acid (122 mL, 144 g) was added under stirring. The vigorously stirred mixture was refluxed for 3 h and then cooled to room temperature. The resulting precipitate was filtered, washed with diethyl ether (200 mL), and dissolved in water (500 mL). The saturated solution of sodium bicarbonate was added to the resultant aqueous solution under stirring until pH value of the reaction mixture was 8. Sodium chloride (50 g) was added and the reaction mixture was stirred for 3 h. The resulting precipitate was filtered, washed with water until pH 7, dried in a desiccator over sodium hydroxide. The crude product was purified by recrystallization from diethyl ether, to give the pure diamine **4** as a colourless solid; yield 13.5 g (78%). Characterization data for **4** are consistent with values previously reported.[18]

4.2.3. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-diisocyanato-4-carboxylic acid methyl ester *3*

Following the above procedure, the crude reaction mixture in toluene solution (about 50 mL) was obtained from **2** (2 g, 4.6 mmol) after Curtius rearrangement (after reflux until the nitrogen evolution has stopped). The reaction mixture was cooled to room

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temperature. Toluene was removed under reduced pressure yielding the crude product, which was purified by column chromatography (hexane/ethyl acetate = 20:1) to give diisocyanate **3** as a colourless oil; yield: 1.35 g (69%); R_f = 0.9 (hexane/ethyl acetate = 20:1), $[\alpha]_D^{25}$: +61,5 (*c* 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.58 (s, 3H), 0.93 (m, 1H), 1.01–1.05 (m, 6H), 1.12–1.18 (m, 4H), 1.23–1.31 (m, 3H), 1.41–1.53 (m, 5H), 1.68 (m, 2H), 1, 89 (m, 1H), 2.04 (m, 1H), 2.33 (m, 1H), 2.56 (m, 1H), 2.87 (m, 1H), 3.24 (m, 1H), 3.63 (s, 3H), 5.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$: δ = 178.9, 148.4, 123.5, 122.9, 122.4, 69.9, 62.4, 51.8, 51.7, 49.2, 47.0, 43.4, 39.6, 37.8, 37.1, 36.5, 33.7, 32.5, 21.4, 21.1, 20.3, 20.2, 16.9, 16.6, 15.6 ppm. IR (KBr): 2933, 2870, 2240, 1725, 1465, 1447, 1387, 1362, 1246, 1188, 1140 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{25}H_{34}N_2O_4$ 426.2513, found 426.2511.

4.3. General procedure for the synthesis of imines **5a-f**

The corresponding aldehyde (Scheme 2) (5.3 mmol) was added to a stirring solution of diamine **4** (1 g, 2.7 mmol) in chloroform (20 mL). The reaction mixture was refluxed for 8 h, then the solvent was removed under reduced pressure yielding the crude imines ***5a-f***. Imines ***5b, e, f*** were purified by column chromatography (SiO_2, hexane/ethyl acetate = 8:2). Imines ***5a, c, d*** were purified by crystallization from ethanol.

4.3.1. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(2-hydroxybenzylideneamino)-4-carboxylic acid methyl ester **5a**

Imine **5a** was prepared from salicylic aldehyde as a yellow solid purified by crystallization; yield 89%, R_f = 0.6 (hexane/ethyl acetate = 7:3), m.p. 133–135 °C, $[\alpha]_D^{25}$: +330.0 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (s, 3H), 1.05 (m, 2H), 1.12 (m, 7H), 1.17 (m, 4H), 1.55 (m, 6H), 1.75 (m, 3H), 2.18 (m, 1H), 2.46 (m, 1H), 2.56 (m, 1H), 2.92 (d, *J* = 2.2 Hz, 1H), 3.06 (m, 1H), 3.66 (s, 3H), 5.59 (s, 1H), 6.83–7.01 (m, 4H), 7.19–7.37 (m, 4H), 8.15 (s, 1H), 8.27 (s, 1H), 13.43 (br s, 1H), 13.53 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 164.6, 163.6, 161.3, 161.2, 147.9, 132.6, 132.4, 131.6, 131.5, 125.4, 118.9, 118.8, 118.6, 118.6, 117.1, 117.09, 85.5, 76.7, 53.3, 52.0, 49.9, 47.4, 42.3, 40.8, 38.3, 37.7, 37.0, 34.9, 32.9, 22.2, 21.9, 20.87, 20.85, 17.3, 16.9, 16.3. IR (KBr): 2929, 2868, 1723, 1626, 1579, 1494, 1460, 1386, 1280, 1244, 1194, 1150, 1071, 1049, 846, 757 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{37}H_{46}N_2O_4$ 582.3457, found 582.3456.

4.3.2. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(2-hydroxy-3-methoxybenzylideneamino)-4-carboxylic acid methyl ester **5b**

Imine **5b** was prepared from 3-methoxy-2-hydroxy benzaldehyde as a yellow solid purified by chromatography; yield 79%, R_f = 0.33 (hexane/ethyl acetate = 7:3), m.p. 138–139 °C, $[\alpha]_D^{25}$: +402 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (s, 3H), 1.00 (m, 2H), 1.08 (m, 7H), 1.12 (m, 4H), 1.41–1.54 (m, 6H), 1.69 (m, 3H), 2.17 (m, 1H), 2.41 (m, 1H), 2.53 (m, 1H), 2.86 (d, *J* = 1.7 Hz, 1H), 3.02 (m, 1H), 3.62 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 5.53 (s, 1H), 6.74–6.94 (m, 6H), 8.08 (s, 1H), 8.21 (s, 1H), 13.86 (br s, 1H), 14.16 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 164.3, 163.5, 151.8, 151.4, 148.3, 148.3, 147.7, 125.0,122.8, 122.7, 118.3, 118.1, 118.0, 117.8, 113.8, 113.41, 85.0, 76.0, 55.9, 55.8, 53.0, 51.8, 49.6, 47.1, 42.0, 40.2, 37.9, 37.4, 36.8, 34.5, 32.7, 21.9, 21.6, 20.6, 20.5, 17.0, 16.6, 15.3. IR (KBr): 2934, 2867, 1721, 1624, 1584, 1463, 1417, 1386, 1254, 1080, 973, 841, 781, 738 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{39}H_{50}O_6N_2$ 642.3652, found 642.3663.

4.3.3. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(2-hydroxy-3,5-di-tert-butylbenzylideneamino)-4-carboxylic acid methyl ester **5c**

Imine **5c** was prepared from 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as a light yellow solid purified by crystallization; yield 78%, R_f = 0.62 (hexane/ethyl acetate = 7:3), m.p. 191–192 °C, $[\alpha]_D^{25}$: +289 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (s, 3H), 1.17 (m, 7H), 1.22 (m, 3H), 1.32 (m, 21H), 1.50 (m, 24H), 1.82 (m, 3H), 2.25 (m, 1H), 2.53 (m, 1H), 2.58 (m, 1H), 2.97 (m, 1H), 3.04 (m, 1H), 3.69 (s, 3H), 5.66 (s, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.40 (s, 1H), 7.45 (s, 1H), 8.20 (s, 1H), 8.31 (s, 1H), 13.48 (br s, 1H), 13.68 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 165.2, 164.1, 157.7, 157.5, 147.1, 139.8, 139.4, 136.2, 136.2, 126.6, 126.3, 125.8, 125.6, 125.0, 117.5, 117.2, 84.8, 76.9, 53.0, 51.5, 49.4, 46.9, 41.8, 40.1, 37.7, 37.2, 36.5, 34.7, 34.7, 34.3, 33.7, 33.7, 32.4, 31.1 (6 CH_3), 29.1 ($3CH_3$), 29.0 ($3CH_3$), 21.7, 21.5, 20.4, 20.3, 16.8, 16.3, 15.9 ppm. IR (KBr): 2954, 2869, 1721, 1624, 1595, 1467, 1441, 1387, 1361, 1272, 1248, 1173 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{53}H_{78}N_2O_4$ 806.5956, found 806.5953.

4.3.4. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(2-hydroxy-1-naphthylmethyleneamino)-4-carboxylic acid methyl ester **5d**

Imine **5d** was prepared from 2-hydroxy-1-naphthaldehyde as a yellow solid purified by crystallization; yield 74%, R_f = 0.38 (hexane/ethyl acetate = 7:3), m.p. 162–164 °C, $[\alpha]_D^{25}$: +239.8 (*c* 0.5, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 1.07 (m, 1H), 1.14 (m, 11H), 1.24 (m, 1H), 1.49 (m, 4H), 1.62 (m, 2H), 1.80 (m, 3H), 2.20 (m, 1H), 2.51 (m, 1H), 2.68 (m, 1H), 3.13 (m, 1H), 3.34 (m, 1H), 3.62 (s, 3H), 5.63 (s, 1H), 6.93–7.94 (m, 12H), 8.69 (s, 1H), 8.95 (s, 1H), 14.55 (br s, 1H), 15.28 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 173.7, 169.6, 159.1, 157.3, 149.1, 136.7, 136.0, 133.2, 132.7, 129.0 (2CH), 127.8 (2CH), 126.8, 126.3, 124.3, 123.5, 123.1, 122.8, 121.9, 118.6, 118.2, 107.7, 106.6, 80.6, 73.9, 52.8, 51.8, 49.4, 47.0, 42.4, 40.3, 37.9, 37.4, 36.7, 34.3, 32.7, 21.7, 21.5, 20.6, 20.6, 16.9, 16.5, 15.8 ppm. IR (KBr): 2928, 2867, 1722, 1624, 1545, 1473, 1336, 1245, 1183, 1140, 826, 747 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{45}H_{50}O_4N_2$ 682.3765, found 682.3760.

4.3.5. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(2′-pyridyl-methyleneamino)-4-carboxylic acid methyl ester **5e**

Imine **5e** was prepared from 2-pyridinecarbaldehyde as a off-yellow viscous syrup purified by chromatography; yield 81%, R_f = 0.22 (hexane/ethyl acetate = 3:7), $[\alpha]_D^{25}$: +165.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 0.88 (m, 1H), 1.00 (m, 1H), 1.07 (m, 12H), 1.28 (m, 1H), 1.48 (m, 4H), 1.62 (m, 2H), 1.72 (m, 2H), 2.30 (m, 1H), 2.43 (m, *J* = 6.8 Hz, 1H), 2.48 (m, 1H), 3.04 (m, 1H), 3.07 (m, 1H), 3.59 (s, 3H), 5.53 (s, 1H), 7.22 (m, 2H), 7.67 (m, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 8.12 (s, 1H), 8.19 (s, 1H), 8.54 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.3, 161.0, 160.5, 154.6, 154.5, 149.1, 149.0, 146.7, 136.3, 136.2, 125.5, 124.4, 124.3, 121.3, 121.2, 85.7, 76.6, 54.0, 51.7, 49.7, 47.2, 42.2, 40.7, 37.8, 37.5, 36.7, 34.5, 32.5, 21.8, 21.8, 20.5, 20.4, 17.0, 16.6, 16.3 ppm. IR (KBr): 2928, 2867, 1722, 1641, 1587, 1567, 1468, 1436, 1384, 1360, 1245, 1187, 1142, 1073, 992, 916, 776, 733 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{35}H_{44}N_2O_4$ 552.3459, found 552.3460.

4.3.6. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(thioph-2-ylidenamino)-4-carboxylic acid methyl ester **5f**

Imine **5f** was prepared from 2-thiophenecarbaldehyde as a off-yellow solid purified by chromatography; yield 68%; R_f = 0.53 (hexane/ethyl acetate = 7:3), m.p. 108–109 °C; $[\alpha]_D^{25}$: +258,9 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 1.00 (m, 2H), 1.08 (m, 8H), 1.15 (s, 3H), 1.50 (m, 6H), 1.73 (m, 3H), 2.28 (m, 1H), 2.42 (m, 2H), 2.86 (m, 1H), 2.93 (m, 1H), 3.62 (s, 3H), 5.51 (s, 1H), 6.98–7.03 (m, 2H), 7.20 (m, 2H), 7.29 (m, 1H), 7.34 (m, 1H), 8.12 (s, 1H), 8.20 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.3, 152.8, 152.3, 146.4, 143.0, 142.7, 129.8, 129.5, 128.2, 128.0, 127.1, 127.0, 125.5, 85.7, 76.7, 54.0, 51.6, 49.8, 47.2, 42.3, 40.8, 37.8, 37.5, 36.8, 34.6, 32.5, 21.9, 21.7, 20.6, 20.4, 17.0, 16.5, 16.3 ppm. IR (KBr): 3089, 2947, 2865, 1719, 1673, 1626, 1518, 1419, 1234, 1214, 1046, 757, 728,

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662 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{33}H_{42}N_2O_2S_2$ 562.2682, found 562.2675.

4.4. General procedure for the synthesis of Aminophenols **6a-f**

Sodium borohydride (150 mg, 4 mmol) was added portion wise to a stirred solution of the corresponding imine **5 a-f** (1 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred at room temperature for 8 h and concentrated under reduced pressure. Then 10 mL of water was added to the residue and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 7:3).

4.4.1. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di[(2-hydroxybenzyl)amino]-4-carboxylic acid methyl ester **6a**

Aminophenol **6a** was prepared from imine **5a** as a colourless solid; yield 96%, %, R_f = 0.32 (hexane/ethyl acetate = 7:3), m.p. 178–179 °C, $[\alpha]_D^{25}$: +16.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (s, 3H), 0.96 (m, 1H), 1.02 (m, 6H), 1.06 (m, 1H), 1.16 (s, 3H), 1.20 (m, 1H), 1.30 (m, 1H), 1.42 (m, 4H), 1.53 (m, 2H), 1.71 (m, 2H), 1.82 (m, 1H), 2.02 (m, 1H), 2.15 (m, 1H), 2.30 (m, 1H), 2.41 (m, 1H), 2.75 (m, 1H), 3.66 (s, 3H), 3.83 (d, *J* = 13.6 Hz, 1H), 3.89 (d, *J* = 13.6 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 5.40 (s, 1H), 6.74 (m, 1H), 6.81 (m, 2H), 6.88 (m, 1H), 6.97 (m, 1H), 7.03 (m, 1H), 7.14 (m, 1H), 7.20 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4, 158.7, 158.3, 149.5, 129.5, 129.3, 128.8, 128.7, 124.8, 123.1, 123.07, 119.8, 119.5, 116.9, 116.8, 73.7, 63.6, 53.8, 52.3, 50.8, 50.3, 49.8, 47.6, 43.0, 38.8, 37.9, 37.2, 35.9, 34.9, 33.1, 22.2, 21.6, 21.0, 20.8, 17.5, 17.2, 16.2. IR (KBr): 3282, 2926, 2865, 1708, 1612, 1590, 1476, 1446, 1387, 1248, 1193, 1139, 1104, 845, 797, 752 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{37}H_{50}N_2O_4$ 586.3765, found 586.3768.

4.4.2. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di[(2-hydroxy-3-methoxybenzyl)amino]-4-carboxylic acid methyl ester **6b**

Aminophenol **6b** was prepared from imine **5b** as a off-yellow solid; yield 71%, R_f = 0.1 (hexane/ethyl acetate = 7:3), m.p. 83–85 °C, $[\alpha]_D^{25}$: +37.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.64 (s, 3H), 0.95 (m, 1H), 1.02 (m, 6H), 1.08 (m, 1H), 1.15 (m, 4H), 1.34 (m, 1H), 1.44 (m, 4H), 1.55 (m, 1H), 1.70 (m, 2H),1.88 (m, 1H), 2.04 (m, 1H), 2.20 (m, 1H), 2.33 (m, 1H), 2.42 (m, 1H), 2.76 (m, 1H), 3.68 (s, 3H), 3.87 (s, 3H), 3.90 (m, 6H), 4.09 (d, *J* = 13.3 Hz, 1H), 5.39 (s, 1H), 6.55–6.88 (m, 6H), 10.38 (br s, 1H), 11.01 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7, 148.6, 147.8, 147.7, 147.0, 146.3, 123.8, 123.9, 122.4, 120.2, 119.8, 118.6, 118.2, 110.7, 110.5, 72.9, 62.9, 55.5, 55.3, 52.9, 51.6, 49.4, 48.9, 46.7, 42.0, 37.8, 36.9, 36.2, 35.1, 34.0, 32.2, 21.3, 20.7, 20.1, 20.0, 16.7, 16.3, 15.3 ppm. IR (KBr): 2932, 2865, 1721, 1645, 1588, 1477, 1245, 1187, 1076, 975, 833, 771, 733 cm^{-1}. Elemental analysis (%): calcd. for $C_{37}H_{50}N_2O_4$ C 72.41, H 8.41, N 4.33; found C 72.44, H 8.39, N 4.35.

4.4.3. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di[(2-hydroxy-3,5-di-tert-butylbenzyl)amino]-4-carboxylic acid methyl ester **6c**

Aminophenol **6c** was prepared from imine **5c** as a colourless solid; yield 77%, R_f = 0.63 (hexane/ethyl acetate = 7:3), m.p. 130–132 °C, $[\alpha]_D^{25}$: −31.4 (*c* 0.051, CH_3COCH_3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64 (s, 3H), 0.93 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.07 (m, 1H), 1.16 (s, 3H), 1.19 (m, 1H), 1.25 (m, 9H), 1,28 (m, 2H), 1.30 (m, 1H), 1.31 (s, 9H), 1.39 (m, 2H), 1.44 (m, 18H), 1.48 (m, 2H), 1.53 (m, 2H), 1.70 (m, 2H), 1.82 (m, 1H), 1.96 (m, 1H), 2.18 (m, 1H), 2.30 (m, *J* = 6.6 Hz, 1H), 2.39 (m, 1H), 2.74 (m, 1H), 3.66 (s, 3H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.94 (d, *J* = 13.6 Hz, 1H), 4.01 (d, *J* = 13.6 Hz, 1H), 4.11 (d, *J* = 13.6 Hz, 1H), 5.38 (s, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 2.2 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 10.70 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 154.6, 154.1, 149.0, 140.7, 140.5, 135.9, 135.8, 124.2, 123.4, 123.2, 123.1, 122.9, 121.9, 121.8, 71.8, 63.1, 53.2, 51.8, 51.0, 49.5, 49.0, 47.1, 42.2, 38.1, 37.2, 36.5, 35.1, 34.8, 34.7, 34.3, 34.0, 34.0, 32.6, 31.6 ($3CH_3$), 31.5 ($3CH_3$), 30.0 ($3CH_3$), 29.4 ($3CH_3$), 21.8, 21.0, 20.4, 20.2, 17.0, 16.7, 15.6 ppm. IR (KBr): 2953, 2868, 1727, 1480, 1461, 1444, 1389, 1361, 1237, 1164, 876 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{53}H_{82}O_4N_2$ 810.6269, found 810.6265.

4.4.4. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di[(2-hydroxynaphthalen-1-yl)methylamino]-4-carboxylic acid methyl ester **6d**

Aminophenol **6d** was prepared from imine **5d** as a colourless solid; yield 79%, R_f = 0.37 (hexane/ethyl acetate = 7:3), m.p. 99–101 °C, $[\alpha]_D^{25}$: +39.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (s, 3H), 0.92 (m, 6H), 1.04 (m, 2H), 1.17 (m, 3H), 1.22 (m, 1H), 1.37 (m, 1H), 1.47 (m, 4H), 1.56 (m, 2H), 1.74 (2H), 1.90 (m, 1H), 2.12 (m, 1H), 2.24 (m, 2H), 2.56 (m, 1H), 2.87 (m, 1H), 3.69 (s, 3H), 4.12 (d, *J* = 14.3 Hz, 1H), 4.44 (d, *J* = 14.3 Hz, 1H), 4.54 (d, *J* = 14.3 Hz, 1H), 4.59 (d, *J* = 14.3 Hz, 1H), 5.43 (s, 1H), 7.04–7.96 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1, 156.7, 156.4, 149.0, 132.2, 132.0, 129.4, 129.2, 128.9, 128.6, 128.5, 128.2, 126.5, 126.4, 124.2, 122.5, 122.4, 120.8 (2CH), 119.2, 119.1, 112.3, 112.2, 73.3, 62.6, 53.1, 52.0, 49.2, 47.1, 44.3, 44.2, 42.4, 38.1, 37.3, 36.6, 35.3, 34.3, 32.5, 21.7, 21.1, 20.3, 20.2, 17.0, 16.7, 15.7 ppm. IR (KBr): 2929, 2867, 1721, 1622, 1598, 1519, 1467, 1268, 1240, 1163, 1102, 814, 745 cm^{-1}. Elemental analysis (%): calcd. for $C_{37}H_{50}N_2O_4$ C 78.68, H 7.92, N 4.08; found C 78.71, H 7.90, N 4.10.

4.4.5. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di[(2-pyridylmethyl)amino]-4-carboxylic acid methyl ester **6e**

Aminophenol **6e** was prepared from imine **5e** as a off-yellow viscous syrup; yield 77%, R_f = 0.2 (hexane/ethyl acetate = 3:7), $[\alpha]_D^{25}$: +3.1 (*c* 0.98, $CHCl_3$). ^{1}H NMR (400 MHz $CDCl_3$): δ = 0.56 (s, 3H), 0.82 (m, 2H), 0.93 (m, 6H), 1.07 (m, 4H), 1.25 (m, 2H), 1.35 (m, 3H), 1.43 (m, 2H), 1.60 (m, 2H), 1.90 (m, 2H), 2.13 (m, 1H), 2.26 (m, 2H), 2.55 (m, 1H), 3.58 (s, 3H), 3.75 (d, *J* = 14.3 Hz, 1H), 3.79 (d, *J* = 14.0 Hz, 1H), 3.83 (d, *J* = 14.3 Hz, 1H), 3.93 (d, *J* = 14.0 Hz, 1H), 5.34 (s, 1H), 7.06 (m, 2H), 7.30 (m, 2H), 7.54 (m, 2H), 8.42 (m, 1H), 8.47 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 16.5, 16.9, 20.2, 20.4, 20.7, 21.8, 32.5, 34.2, 35.6, 36.6, 37.2, 37.8, 42.7, 47.0, 49.5, 51.6, 52.3, 53.1, 53.6, 64.7, 72.8, 121.5, 121.6, 122.2, 122.3, 124.4, 136.1, 136.2, 147.6, 148.7, 148.9, 159.8, 160.3, 179.3 ppm. IR (KBr): 619, 664, 755, 847, 994, 1048, 1104, 1140, 1189, 1246, 1294, 1341, 1361, 1387, 1433, 1473, 1570, 1592, 1642, 1724, 2846, 2867, 2947, 3313 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{35}H_{48}O_2N_4$ 556.3772, found 556.3762.

4.4.6. 13-Isopropyl-17,18-dinor-atis-13-ene-15β,16α-di(((thiophen-2-yl)-methyl)amino)-4-carboxylic acid methyl ester **6f**

Aminophenol **6f** was prepared from imine **5f** as a colourless solid; yield 81%, R_f = 0.5 (hexane/ethyl acetate = 7:3), m.p. 75–77 °C, $[\alpha]_D^{25}$: +61 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (s, 3H), 0.89 (m, 2H), 0.99 (m, 6H), 1.13 (m, 4H), 1.28 (m, 1H), 1.41 (m, 4H), 1.50 (m, 2H), 1.67 (m, 2H), 1.88 (m, 2H), 2.17 (m, 1H), 2.29 (m, 2H), 2.57 (m, 1H), 3.66 (s, 3H), 3.82 (d, *J* = 14.3 Hz, 1H), 3.90 (d, *J* = 14.3 Hz, 2H), 4.04 (d, *J* = 14.3 Hz, 1H), 5.36 (s, 1H), 6.83–6.94 (m, 4H), 7.13–7.19 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 147.9, 145.5, 144.3, 126.3, 126.2, 124.5, 124.5, 124.04, 124.01, 123.9, 72.1, 64.0, 53.6, 51.6, 49.4, 47.0, 45.7, 45.3, 42.7, 37.9, 37.2, 36.6, 35.6, 34.3, 32.5, 21.8, 20.8, 20.5, 20.3, 16.9, 16.6, 15.8 ppm. IR (KBr): 3105, 3070, 2983, 2947, 2868, 2829, 1721, 1458, 1443, 1387, 1368, 1331, 1246, 1215, 1190, 1165, 1140, 1104, 1079, 851, 827, 758,

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698 cm^{-1}. HRMS ESI $[M]^+$ calcd. for $C_{33}H_{46}O_2N_2S_2$ 566.2995, found 566.2988.

4.5. General procedure for the enantioselective Henry reaction

Chiral ligand **6a-f** (20 μmol) was added to the solution of $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 20 μmol) in THF (2 mL). Reaction mixture was stirred for 1 h to give an olive green or dark blue solution, then aldehyde **7a-o** (0.4 mmol) was added followed by the amine or phenol addition in a given quantity (if additives were used, see Tables S1–S3). The reaction mixture was cooled to the selected temperature (see Tables 2, S1–S3) and nitromethane (214 μL, 4 mmol) was added. The mixture was stirred for the selected period from 8 h to 240 h (see Tables 1 and 2, S1–S3), then solvent was removed under reduced pressure, residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 8:2) to give the pure product. The product was analyzed by HPLC and ^1H NMR. The characterization data for all enantiomers of the nitro alcohols were in accordance with data published previously.[23,72–74]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.11.059.

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