Synthesis and analytical resolution of chiral pyrazoles derived from (5*R*)-dihydrocarvone†

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In the course of the development of chiral hydrotris(pyrazolyl)borate ligands for unidirectional molecular machines, we have investigated the preparation of original chiral pyrazoles using (5*R*)-dihydrocarvone as starting material. Of the two synthetic routes examined and described in this article, the most efficient one involved the formation of the pyrazole ring in a last step. This method appeared very efficient and granted access to a pyrazole functionalized with an ester group for subsequent deposition of the corresponding tris(pyrazolyl)borate on insulating oxide surfaces. Analytical HPLC confirmed the presence of a mixture of four diastereoisomers.

Introduction

The hydrotris(pyrazolyl)borate ligands discovered by Trofimenko in the late sixties[1] have been used increasingly in bio-inorganic, organometallic and coordination chemistry.[2] Modification of the functional groups connected to the pyrazolyl moiety in order to control or modify the steric and electronic environment surrounding the metal centre gave rise to extended studies. However, only a few chiral analogues have been studied.[3] Chiral pyrazoles are interesting precursors for the preparation of C_3-symmetrical hydrotris(pyrazolyl)borate ligands which may be used for instance in asymmetric catalysis.[4] Such tripodal ligands have also a potential interest in the design of molecular machines developed recently in our group to prepare organometallic molecular turnstiles[5] or as a building block in the synthesis of a family of surface-mounted electrically-driven molecular motors[6] (Fig. 1) where the hydrotris(indazolyl)borate tripodal ligand[7] has been used.

In order to conceive a unidirectional rotation in a molecular machine, which is still a challenge nowadays, a strong dissymmetrization of the two directions of rotation is required. In agreement with the second principle of thermodynamics, chirality alone is not sufficient to achieve this goal.[8] However, the combination of chirality and an external energy source[9] could be a very efficient way to highly dissymmetrize the system and obtain such a controlled unidirectional motion.[10] Since single molecular rotary motors require a unidirectional rotation, the use of a chiral hydrotris(pyrazolyl)borate stator is therefore of major interest to favour one direction of motion over the opposite one, as already seen in synthetic molecular motors[11] or in biological motors such as ATP synthase.[12]

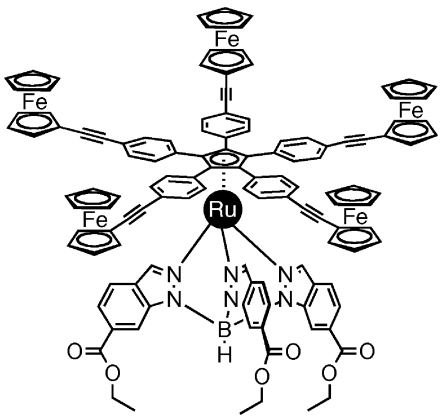

Fig. 1 Prototype of a molecular motor with a symmetric tripodal ligand. The ruthenium center is coordinated to a hydrotris(indazolyl)borate ligand and to a penta(4-(ethynylferrocenyl)phenyl)cyclopentadienyl ligand.

In this context, we studied the synthesis of enantiopure chiral pyrazoles for the preparation of C_3-symmetrical hydrotris(pyrazolyl)borate ligands. For this purpose, we focussed on pyrazoles derived from (5*R*)-dihydrocarvone **1**, commercially available as a (2*R*,5*R*) and (2*S*,5*R*) diastereomeric mixture from the chiral pool. Its olefin moiety was converted into an ester function for the future immobilization of the molecular motor onto insulating oxide surfaces. We present here the synthesis of chiral pyrazoles following two different routes as well as their analytical resolution.

Results and discussion

Molecular modelling

Molecular modelling was performed on the ruthenium complex with Cerius2 (Fig. 2, right) in order to check that the target tris(pyrazolyl)borate coordinated to the ruthenium

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† Dedicated to Prof. Jean-Pierre Sauvage on the occasion of his 65th birthday.

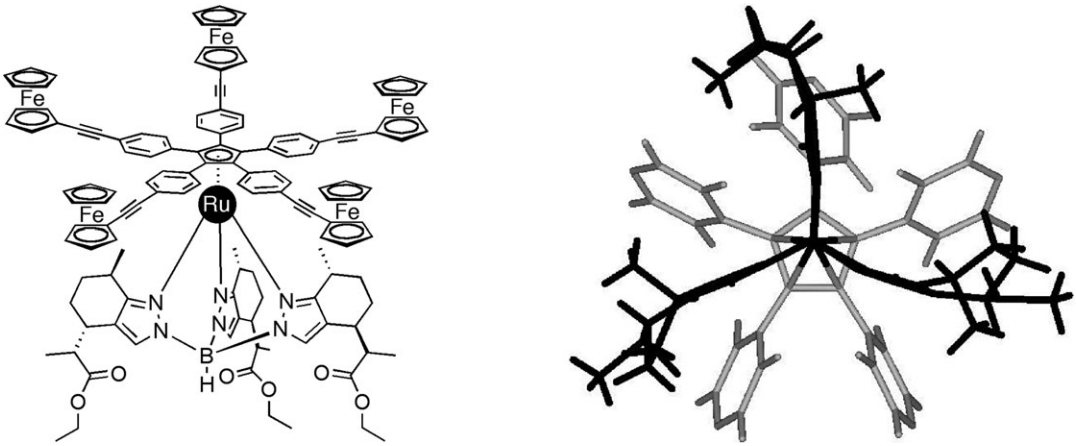
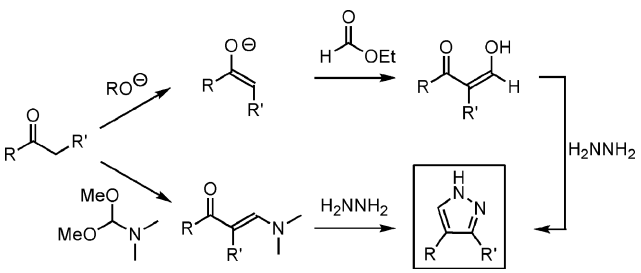


Fig. 2 Chemical structure (left) and molecular modelling (right, bottom view) of a the ruthenium complex integrating a chiral hydrotris(pyrazolyl)-borate ligand. The modeling has been performed on the full molecule but to obtain a clear representation, the ester and the ethynylferrocenyl fragments have been omitted. The modelling clearly show the induced helicity of the molecule in the minimum energy conformation (Universal Force Field, Cerius2 software[13]).

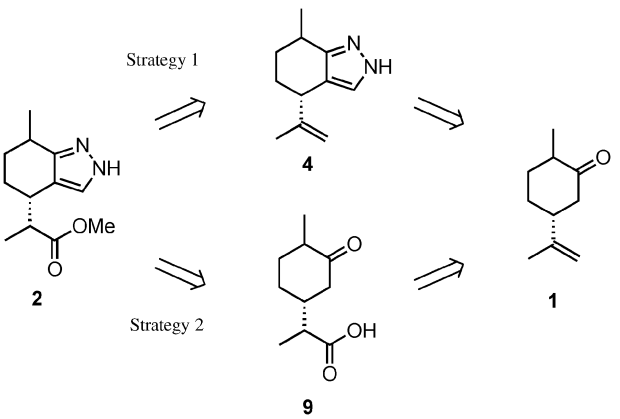
center (Fig. 2, left) would indeed induce the desired helicity once coordinated.[13] The chirality of the tripodal ligand, and particularly the methyl groups at the 4-position of the ring, strongly interact with the cyclopentadienyl ligand, which is the key to induce a strong dissymmetry in the system. The use of (5*R*)-dihydrocarvone as starting material seems particularly appropriate to bring chirality through the helicity of the C_6-fused ring and will simultaneously allow to build the pyrazole heterocycle through its carbonyl function.

Two strategies are usually followed to build a pyrazole ring, both starting from an enolisable ketone (Scheme 1). The first one is based on a Claisen formylation with ethyl methanoate. In the following step, the β-ketoaldehyde formed is reacted with hydrazine to yield the pyrazole ring.[14] The second strategy introduces the enamine function, precursor of the pyrazole ring, by reaction with DMF–dimethylacetal.[15] After purification, the intermediate is cyclized by reaction with hydrazine yielding the pyrazole ring. It must be noted that these strategies are compatible with a large variety of chiral substrates.

From a retrosynthetic point of view, the preparation of the hydrotris(pyrazolyl)borate ligand requires the synthesis of the optically pure ester pyrazole (**2**). The latter can be prepared following two different routes (Scheme 2), which mainly differ by the stage at which the pyrazole ring is constructed, *i.e.* in the first step or in the last step.



Scheme 1 The two most common synthetic strategies to prepare pyrazoles (R and R′ are alkyl or aryl groups).

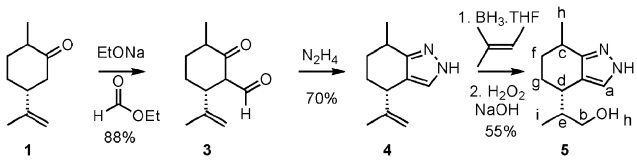


Scheme 2 Retrosynthetic analysis of the required ester pyrazole (**2**).

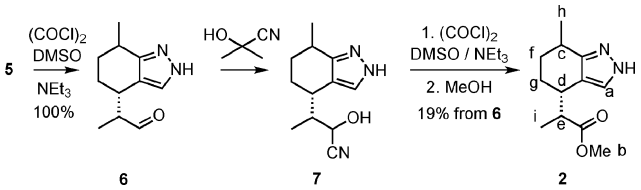
First route

Pyrazole **4** (Scheme 3) was prepared in two steps from (5*R*)-dihydrocarvone (**1**) by a Claisen condensation followed by a cyclization reaction with hydrazine which resulted in a mixture of (4*R*,7*S*) and (4*S*,7*S*) diastereomers.[16] The Claisen formylation was performed by reaction of **1** with sodium ethanolate forming the corresponding enolate. The latter was then involved in an acyl nucleophilic substitution on ethyl methanoate. The literature describes[14] the hereafter obtained β-ketoaldehyde (**3**) as a poorly stable compound. It should be used immediately without any further purification.

The pyrazole cycle was formed subsequently *via* a cyclisation with hydrazine. Pyrazole **4** was obtained with a global yield of 61% starting from **1**. It must be noted that compound



Scheme 3 Synthesis of the pyrazole ring followed by hydroboration–oxidation of the exocyclic double bond.



Scheme 4 Sequential oxidation and functionalization of **5** to yield the ester-functionalized pyrazole (**2**).

4 is not so stable. A slow reduction of the isopropenyl group into an isopropyl group has been observed upon long storage period. The characteristic isopropyl group has been easily identified by ^{1}H NMR and confirmed by mass spectrometry performed on the mixture of stereoisomers.

The conversion of the alkene into the least substituted alcohol was achieved by hydroboration followed by the classical oxidation of the borane formed.[17] Compound **4** was reacted with BH_3 in THF followed by the addition of sodium hydroxide and hydrogen peroxide to give alcohol **5** with a 55% yield. The reaction was performed in the presence of the 2-methylbut-2-ene in order to favour the regioselectivity of the addition[18] by coordination of the alkene on the boron centre, which induces a steric hindrance.

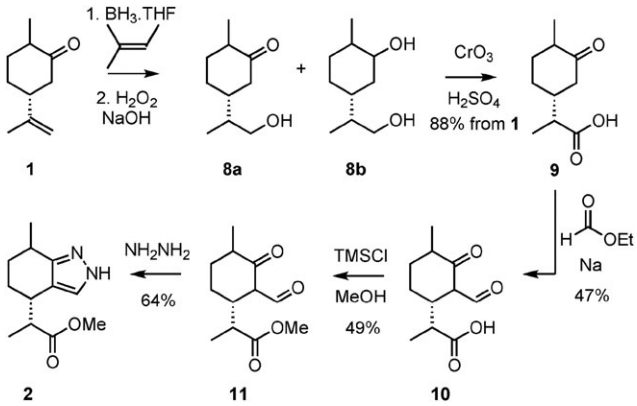
The next step consisted in the conversion of the alcohol function into the corresponding ester. A first attempt to directly oxidize the hydroxy group was performed using the Sarett reagent system (CrO_3 and pyridine in the presence of acetic anhydride and *tert*-butanol).[19] Unfortunately these conditions yielded a decomposition of the pyrazole ring as shown by ^{1}H NMR with the absence of aromatic proton which would be expected for the pyrazole ring. An alternative route using milder conditions (TEMPO/NaOCl/$NaClO_2$)[20] was attempted unsuccessfully. Therefore, we envisaged a multistep oxidation procedure as represented in Scheme 4.[21]

Alcohol **5** was first oxidized into an aldehyde under the mild Swern conditions[22] which preserved the pyrazole ring. Aldehyde **6** was obtained quantitatively and reacted with acetone cyanohydrin in the presence of a catalytic amount of triethylamine. After the quantitative conversion of the aldehyde, the crude cyanohydrin **7** was again oxidized under Swern conditions. After addition of triethylamine, the intermediate was quenched with methanol. The corresponding ester (**2**) was formed with a global yield of 19% from **5** (*i.e.* 66% average yield by step).

Nevertheless, this synthetic strategy showed two drawbacks. Pyrazoles display strong interactions with silica and therefore their purification on column chromatography is difficult on a large scale and is accompanied by an important loss of material on the column as shown by the poor yields. In addition, during the second oxidation step using the Swern conditions, the aldehyde and the ester are difficult to separate. To overcome these obstacles, an alternative route was developed, the key point of this second strategy being the pyrazole ring formation as a last step of the alternative route.

Alternative route

We subsequently investigated another synthetic route involving the formation of the pyrazole ring in the last step. This



Scheme 5 Alternative route to prepare the ester-functionalized pyrazole (**2**).

strategy requires the functionalization of the exocyclic double bond. The hydroboration reaction performed on (5*R*)-dihydrocarvone (**1**), as shown on Scheme 5, gave the desired hydroxyketone (**8a**). Despite the use of 2-methylbut-2-ene in order to minimize the reduction of the carbonyl group,[18] the reduced by-product **8b** was also obtained, possibly due to the high energy of the boron–oxygen bond, the formation of which could constitute the driving force of the side reaction.

However, it is not necessary to separate **8a** from **8b** because the next oxidation step using Jones' reagent (CrO_3, H_2SO_4) performed on the mixture of **8a** and **8b** yields as the unique product the carboxylic acid (**9**). Once **9** is obtained, the formylation reaction is realized using three equivalents of sodium because of the presence of an acidic proton in **9**. It is interesting to notice that the same reaction performed on the methyl ester derivative of **9** gave the corresponding ethyl ester without any formylation product. Therefore, the carboxylic acid **10** can be esterified in the presence of chlorotrimethylsilane in methanol.[23] After column chromatography, **11** was obtained with a global yield of 20% from dihydrocarvone **1** (four steps). The last step of this alternative strategy consisted in the synthesis of the pyrazole ring by reaction of **11** with hydrazine. The desired pyrazole ester **2** was then obtained in a 64% yield.

Following this second strategy, it has been possible to double the overall yield (from 6 to 13%) of the desired pyrazole ester (**2**) but also to facilitate the purification steps.

Since it is not realistic to prepare the tripodal ligand on a mixture of four diastereoisomers, a resolution of the mixture is required before performing the reaction with KBH_4 to yield the optically pure tripodal ligands. If not, the reaction would give a useless mixture of 20 stereoisomers after addition of three pyrazoles on the boron center.

Analytical resolution

To resolve such a mixture, we investigated chromatographic methods. As shown on Fig. 3, analytical resolution of the mixture was achieved using HPLC separation with an apolar column as the stationary phase (*vide infra* for experimental details) and granted access to the proportion of each of the four diastereoisomers.

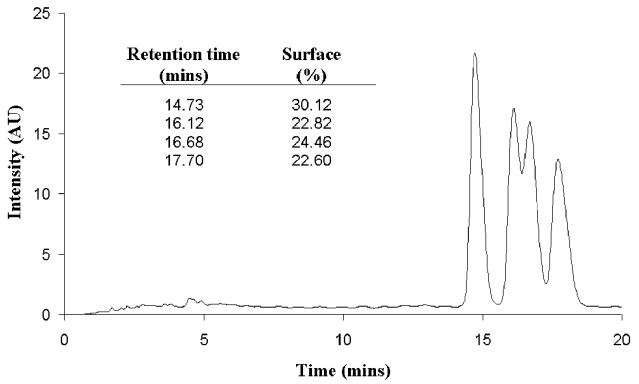


Fig. 3 HPLC chromatogram (Sunfire column C18, 150 mm × 4.6 mm × 5 μm, eluent: H_2O–MeOH 1:1, rate 1 mL min^{-1}) of the analytic resolution of the ester-functionalized pyrazole (**2**) showing the four diastereoisomers and their respective percentages.

The respective amounts are close but different from the statistical distribution, with percentages between 22 and 30% compared to the statistical value of 25%. In the course of the synthesis, the formation of the third chiral center during the hydroboration step could occur with an asymmetric induction.

Up to now, extension of this methodology to the preparative scale did not allow us to obtain pure diastereoisomers, the separation between the four different peaks being too small to yield sufficient amounts of pure material. The major problem seems once again to be the behaviour of pyrazole derivatives on various columns.

Conclusion

In conclusion, the racemic synthesis of chiral pyrazoles has been performed using (5*R*)-dihydrocarvone from the chiral pool as starting material. The first strategy involving the functionalization of a pre-formed pyrazole ring is limited by the difficulties of purification on a large scale and the poor yield of the conversion of the alcohol function into an ester group, in the last step. The second strategy enabled to obtain cleanly the pyrazole functionalized with an ester anchoring group for subsequent deposition of the target tris(pyrazolyl)-borate ruthenium complex on insulating oxide surfaces. Analytic HPLC confirmed the presence of a mixture of four diastereoisomers, with percentages close to the statistical distribution. Work is now underway to develop an asymmetric synthesis of one stereoisomer, focussing on performing the hydroboration step in the presence of a chiral inductor.

Experimental

Materials and methods

All commercially available chemicals were of reagent grade and were used without further purification. (5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone (known as (5*R*)-dihydrocarvone, **1**) and 2-methylbut-2-ene were purchased from Aldrich. Ethyl methanoate and chlorotrimethylsilane were purchased from Acros. Triethylamine was dried over KOH, diethyl ether and THF over sodium with benzophenone and dichloromethane was dried over CaH_2. (6*R*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)-cyclohexanecarbaldehyde (**3**) was prepared according to a literature procedure.[14] (4*S*)-Isopropylidenemethyl-4,5,6,7-tetrahydro-2(1)*H*-indazole (**4**) was prepared as a mixture of two diastereoisomers in two steps according to a literature procedure.[14] The Jones reagent solution (8 N) was prepared by dissolving 26.72 g of CrO_3 in 23 mL of concentrated H_2SO_4 and diluted with water up to 100 mL. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Flash column chromatography was carried out on silica gel 230–400 mesh from SDS.

NMR Spectra were recorded on Bruker Avance 300 or Avance 500 spectrometers and full assignments were made using COSY, ROESY, HMBC and HMQC methods. Chemical shifts are defined with respect to TMS = 0 ppm for ^1H and ^{13}C NMR spectra and were measured relative to residual solvent peaks. The following abbreviations have been used to describe the signals: s for singlet; d for doublet; t for triplet; q for quadruplet; m: for multiplet. The numbering scheme is given in Schemes 3 and 4. FAB and DCI mass spectrometry were performed using a Nermag R10-10. The analytical HPLC experiments were performed on a unit composed of Mass Lynx system manager, Waters 2545 pump, Waters 2767 injector, Waters 2996 UV PDA-detector, and Waters 3100 MS detector. The column used was a Sunfire C18 (150 mm × 4.6 mm 5 μm) from Waters SA (Saint Quentin en Yvelines, France). The eluent was a 1:1 mixture of H_2O and MeOH and the elution rate was 1 mL min^{-1}.

Synthesis

(4*S*)-4-Isopropylidene-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (4). To a sodium suspension (1.5 g, 65 mmol, 2 eq.) in distilled diethylether (250 mL) were added (5*R*)-dihydrocarvone (5.4 mL, 32.8 mmol, 1 eq.) and ethyl methanoate (4 mL, 49 mmol, 1.5 eq.). After one hour, absolute ethanol (1.5 mL) was added to the mixture. The solution was stirred overnight. Additional absolute ethanol (1 mL) was added followed 2 hours later by water (30 mL). The β-ketoaldehyde formed was extracted with ether. The organic layer was washed with water, and the aqueous layers were acidified to pH = 1 by a 33% HCl solution. After a second extraction with ether, the organic layer was dried over magnesium sulfate. Concentration in vacuum gave the crude material which was purified by column chromatography (SiO_2, CH_2Cl_2). The (6*R*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohexanecarbaldehyde (**3**) was obtained pure as an orange oil. The same day, hydrazine monohydrate (3.24 mL, 67 mmol, 2.5 eq.) was added to a solution of the β-ketoaldehyde in methanol (20 mL). The mixture was refluxed overnight. After concentration in vacuum, the product was extracted with dichloromethane and washed with a saturated NaCl solution. After evaporation, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/AcOEt 8:2 then CH_2Cl_2/MeOH 9:1). **4** was obtained as a yellow oil with a yield of 61%. MS (DCI/NH_3): 177 ($[M+H]^+$, 100%, calc. 177); HR-MS (DCI/CH_4): calculated $[M+H]^+$: 177.1392 ($C_{11}H_{17}N_2$), found: 177.1365; ^1H NMR (300 MHz, CD_2Cl_2) δ 12.54 (s, 1H, NH), 7.34 (s, 0.5H, H_a), 7.33 (s, 0.5H, H_a), 5.3–4.8

(m, 2H, H_b), 3.4 (m, 1H, H_d), 3.0–2.9 (m, 1H, H_c), 2.2–1.4 (m, 10H, $H_{f\text{-}g\text{-}h\text{-}i}$); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 164.3; 148.8; 109.0; 46.1; 39.3; 36.3; 32.8; 31.2; 20.6; 16.6.

(4*S*)-(1-methyl-2-hydroxyethyl)-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (5). To a solution of 2-methylbut-2-ene (9 mL, 85 mmol, 15 eq.) in freshly distilled THF (40 mL), a solution of BH_3 (1 M in THF, 212.5 mL, 212.5 mmol, 2.5 eq.) was added under argon at 0 °C. After 2 hours, a solution of **4** (1 g, 5.15 mmol, 1 eq.) in THF (30 mL) was added. The solution was stirred overnight at room temperature. Absolute ethanol (25 mL) followed by an aqueous NaOH solution (4 M, 10 mL) and 30% aqueous H_2O_2 (10 mL) were successively added dropwise at 0 °C. The solution was stirred overnight. After evaporation of the solvent, the product was extracted with dichloromethane and washed with a saturated NaCl solution. After concentration in vacuum, the crude mixture was purified by column chromatography (SiO_2, AcOEt/CH_2Cl_2 8:2). **5** was obtained as a white solid in 54% yield. MS (DCI/NH_3): 195 ($[M+H]^+$, 100%, calc. 195); HR-MS (DCI/CH_4): calculated $[M+H]^+$: 195.1497 ($C_{11}H_{19}N_2O$), found: 195.1476; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.32–7.30 (m, 1H, H_a), 3.67–3.56 (m, 2H, H_b), 2.92–2.87 (m, 1H, H_c), 2.79–2.71 (m, 1H, H_d), 2.00–1.33 (m, 3H, $H_{e\text{-}f\text{-}g}$), 1.28–1.23 (m, 3H, H_h), 0.99–0.78 (m, 3H, H_i); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 130.9; 77.5; 77.4; 77.2; 76.9; 68.0; 66.3; 66.1; 53.8; 53.7; 53.7; 53.6; 53.5; 53.4; 53.3; 53.0; 52.7; 39.8; 39.1; 34.2; 33.2; 30.3; 29.6; 29.3; 28.9; 27.2; 27.1; 23.7; 21.3; 20.6; 20.4; 14.8; 13.0.

(2*S*)-(7-Methyl-4,5,6,7-tetrahydro-2*H*-indazol-4-yl)propanal (6). To an oxalyl chloride solution (0.18 mL, 2.15 mmol, 1.1 eq.) in dichloromethane (4.8 mL), a mixture of DMSO (0.33 mL, 4.68 mmol, 2.4 eq.) in dichloromethane (1 mL) was added dropwise under an argon atmosphere at −60 °C. After 10 min of stirring, a solution of **5** (0.378 g, 1.95 mmol, 1 eq.) in dichloromethane (15 mL) was added at −60 °C *via* a second addition funnel. The mixture was stirred at −60 °C during 15 min. After addition of triethylamine (1.4 mL, 9.87 mmol, 5 eq.), the mixture was allowed to warm to room temperature. Water (6 mL) was then added and the solution was stirred for 10 min. The aqueous layer was extracted with dichloromethane and the organic layers were dried over magnesium sulfate. After concentration, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/AcOEt 7:3). **6** was obtained pure as a yellow oil in a quantitative yield. MS (DCI/NH_3): 193 ($[M+H]^+$, 100%, calc. 193); HR-MS (DCI/CH_4): calculated $[M+H]^+$: 193.1341 ($C_{11}H_{17}N_2O$), found: 193.1324; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.80–9.70 (m, 1H, H_b), 7.30–7.20 (m, 1H, H_a), 3.27–3.07 (m, 1H), 3.00–2.51 (m, 2H), 2.00–1.85 (m, 1H), 1.80–1.50 (m, 2H), 1.50–1.30 (m, 1H), 1.30–1.15 (m, 3H, H_h), 1.10–1.00 (m, 3H, H_i); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 205.3; 205.2; 204.9; 131.8; 131.2; 127.7; 54.3; 53.9; 53.8; 53.8; 53.7; 53.6; 53.4; 53.4; 53.3; 53.1; 52.8; 50.6; 50.5; 50.4; 50.3; 33.5; 33.0; 32.6; 32.4; 32.3; 32.2; 32.0; 31.9; 29.6; 29.3; 28.8; 28.7; 28.3; 28.1; 27.3; 27.2; 27.1; 25.4; 24.6; 22.6; 20.4; 20.3; 19.9; 19.8; 19.6; 19.4; 19.3; 10.7; 10.1; 9.4; 9.2.

(2*R*)-(4-Methyl-3-oxocyclohexyl)propanoic acid (9). To a 2-methylbut-2-ene solution (28.55 mL, 269.9 mmol, 5 eq.) in distilled THF (125 mL), a solution of BH_3 (1 M in THF, 134.5 mL, 134.5 mmol, 2.5 eq.) was added under an argon atmosphere at 0 °C. After 2 h, a (5*R*)-dihydrocarvone solution (8.83 mL, 53.8 mmol, 1 eq.) in THF (50 mL) was added. The mixture was stirred overnight at room temperature. Absolute ethanol (6 mL), followed by a 15% NaOH solution (50 mL) and a 30% aqueous H_2O_2 solution (50 mL) were successively added dropwise at 0 °C. The mixture was stirred overnight. After concentration in vacuum, the aqueous layer was acidified with concentrated HCl and the product extracted with ether, and washed with a saturated NaCl solution. The mixture of alcohols **8a** and **8b** was obtained as a colorless oil used without further purification. The oil was dissolved in acetone (125 mL) and cooled at 0 °C. After addition of Celite (50 g), 15 mL of the Jones reagent solution (8 N) was added dropwise until a brown color remained. After 10 minutes, isopropanol (5 mL) was added. After separation, the aqueous layer was extracted with ether, and washed with water. The organic layers were dried over magnesium sulfate and concentrated in vacuum. **9** was obtained as a yellow oil in 88% yield. MS (DCI/NH_3): 202 ($[M+NH_4]^+$, 100%, calc. 202); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.50–1.80 (m, 6H), 1.65 (q, 1H, J = 7.4 Hz), 1.32 (tq, 1H, J = 12.9 Hz J = 3.1 Hz), 1.17 (td, 3H, J = 6.7 Hz J = 1.9 Hz), 1.06 (dd, 1H, J = 6.9 Hz J = 2.7 Hz), 0.98 (d, 3H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 212.0; 211.9; 181.8; 181.6; 180.6; 76.0; 75.9; 70.7; 45.6; 44.6; 44.5; 44.2; 42.2; 42.1; 39.8; 39.7; 39.4; 36.5; 36.3; 36.2; 36.2; 34.4; 34.3; 33.5; 32.8; 32.7; 30.3; 30.0; 29.6; 28.4; 27.7; 26.8; 25.9; 25.8; 18.0; 17.9; 17.3; 14.1; 13.3; 13.2.

2-((1*R*)-2-Formyl-4-methyl-3-oxocyclohexyl)propanoic acid (10). To a suspension of sodium (0.561 g, 24.4 mmol, 3 eq.) in distilled THF, was added (2*R*)-(4-methyl-3-oxocyclohexyl)-propanoic acid (**9**) (1.5 g, 8.14 mmol, 1 eq.) and ethyl methanoate (1.3 mL, 16.3 mmol, 2 eq.). After 1 h, absolute ethanol (0.5 mL) was also added to the mixture. The solution was stirred overnight at room temperature. Absolute ethanol (0.3 mL) was added again, followed 2 hours later by water (10 mL). After concentration in vacuum, the product was extracted with ether and washed with water. **10** was obtained as a yellow oil in 47% yield. MS (DCI/NH_3): 212 ($[M]^-$, 100%, calc. 212); HR-MS (DCI/CH_4): calculated $[M+H]^+$: 213.1127 ($C_{11}H_{17}O_4$), found: 213.1095; ^{1}H NMR: (300 MHz, CD_2Cl_2) δ 8.65–8.50 (m, 1H, H_a), 2.50–2.30 (m, 1H), 2.20–2.00 (m, 2H), 1.95–1.75 (m, 1H), 1.75–1.50 (m, 2H), 1.30–1.05 (m, 3H), 1.05-0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 206.8; 206.7; 175.7; 175.6; 173.2; 173.1; 101.6; 53.9; 53.8; 51.7; 51.6; 41.8; 41.7; 41.5; 41.3; 37.1; 36.9; 36.1; 35.5; 25.4; 24.8; 14.3; 14.2; 13.3; 12.7.

Methyl 2-((1*R*)-2-formyl-4-methyl-3-oxocyclohexyl)propanoate (11). To a solution of **10** (0.7 g, 3.3 mmol, 1 eq.) in freshly distilled methanol (66 mL), was added chlorotrimethylsilane (1 mL, 7.75 mmol, 2.35 eq.). After stirring overnight at room temperature, the solvent was evaporated in vacuum. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/AcOEt 8:2). **11** was obtained as a white solid in 49% yield. MS (DCI/NH_3): 244 ($[M+NH_4]^+$, 70%, calc. 244); HR-MS LSIL: calculated $[M+H]^+$: 227.1283

($C_{12}H_{19}O_4$), found: 227.1301; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 15.20–15.00 (m, 1H, H_a), 8.64–8.38 (m, 1H, enol), 3.68–3.58 (m, 2H), 2.50–2.20 (m, 2H), 2.15–1.92 (m, 2H), 1.88–1.72 (m, 2H), 1.70–1.60 (m, 1H), 1.40–1.20 (m, 1H), 1.12–1.08 (m, 3H), 1.00–0.91 (m, 3H).

Methyl (2*S*)-(7-methyl-4,5,6,7-tetrahydro-2*H*-indazol-4-yl)-propanoate (2)

First strategy: From **6**. To a solution of **6** (106 mg, 5.5 mmol, 1 eq.) in dichloromethane (10 mL), triethylamine (15 µL, 0.11 mmol, 0.2 eq.) and acetone cyanohydrin (0.1 mL, 0.11 mmol, 2 eq.) were added under an argon atmosphere. After stirring overnight at room temperature, the solvent was evaporated. The cyanohydrin obtained (**7**) was used without further purification. DMSO (185 µL, 2.61 mmol, 4 eq.) was added dropwise at −78 °C to an oxalyl chloride solution (67 µL, 0.78 mmol, 1.2 eq.) in dichloromethane (1.7 mL). After 15 min, a solution of the freshly formed cyanohydrin **7** in dichloromethane (2 mL) was added. After an additional hour at −78 °C, triethylamine was added (0.5 mL, 3.52 mmol, 5.4 eq.). The mixture was stirred 10 min at −78 °C, and then 15 min at −25 °C. After addition of methanol (0.9 mL), the mixture was stirred overnight at room temperature. The mixture was poured in water (30 mL), and the aqueous layer was extracted with chloroform. The organic layers were dried over magnesium sulfate, concentrated in vacuum and the crude product purified by column chromatography (SiO_2, CH_2Cl_2/AcOEt 8:2). **2** was obtained as a yellow oil in an overall 19% yield from **5**.

Second strategy: Formation of the pyrazole ring from **11**. Hydrazine monohydrate (86 µL, 1.77 mmol, 2.5 eq.) was added to a solution of **11** (161 mg, 0.711 mmol, 1 eq.) in methanol (6.5 mL). The mixture was refluxed overnight. After concentration in vacuum, the product was extracted with dichloromethane and washed with a saturated NaCl solution. After evaporation, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/AcOEt 1:1). **2** was obtained as a yellow oil in 64% yield. MS (DCI/NH_3): 223 ($[M+H]^+$, 100%, calc. 223); HR-MS LSI: calculated $[M+H]^+$: 223.1447 ($C_{12}H_{19}N_2O_2$), found: 223.1488 ($[M+H]^+$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.25 (4 s, 1H, H_a), 3.67 (3 s, 3H, H_b), 3.10–2.50 (m, 3H, H_{c-d-e}), 2.10–1.79 (m, 2H, H_f), 1.79–1.30 (m, 2H, H_g), 1.27 (3 d, 3H, H_h), 1.01 (4 d, 3H, H_i); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 176.7; 176.5; 176.4; 117.0; 116.8; 115.5; 51.5; 51.4; 44.3; 44.9; 43.8; 43.3; 35.7; 35.2; 34.8; 34.5; 31.7; 31.6; 28.9; 28.6; 28.5; 27.8; 27.6; 25.2; 23.1; 20.4; 20.3; 19.8; 19.7; 15.0; 14.1; 13.2; 12.8.

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