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Scientific Research

Synthesis, Resolution and Absolute Configuration of 2,3-Dihydro-2-*Tert*-Butyl-3-*N*-Benzylquinazolin-4-One: A Possible Chiral Auxiliary for Synthesis of *β*-Amino Cyclohexancarboxylic Acid

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Abstract

3-Benzyl-2-(*tert*-butyl)-2,3-dihydroquinazolin-4(1*H*)-one *rac*-11 was resolved via the preparation of diastereomers with *N*-phthalyl-*L*-alanine chloride and its absolute configuration was determined by X-ray crystallographic analysis. This heterocycle has potential as a substrate chiral in asymmetric induction due to the steric effects of its *tert*-butyl group.

Keywords

Chiral Auxiliary; 2-Tert-Butyl-Quinazolin-4-One

1. Introduction

2,3-Dihydro-4(1*H*)-quinazolinones form an important class of bioactive compounds and these can easily be oxidized to their quinazolin-4(3*H*)-one analogues [1]. In general, the derivatives of the quinazolinones are considered as important building blocks [2] [3] for a large number of diverse alkaloids [4] [5] and present a wide range of biological and pharmaceutical activities [6]-[9].

On the other hand, recently an efficient method for the conversion of anhydride isatoic into 4(3*H*)-quinazolinone **1** was described using (*S*)-*α*-methylbenzylamine as chiral auxiliary. Enantiomerically pure quinazolinone

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1 was reduced diastereoselectively by hydrogenation with PtO_2, resulting in octahydroquinazolinone diastereomers. Both *cis*-annelated derivatives (**2** and **3**) could be epimerized in the presence of *t*-BuO^-K^+, giving the corresponding *trans*-fused derivatives (**4** and **5**) respectively in good yields (**Scheme 1**) [10]-[12].

Subsequently, the hydrolysis with HCl 6N of the four adducts (**2**-**5**) affords all four enantiomers of *cis*- and *trans*-2-aminocyclohexanecarboxylic acid (**6**-**9**) in good yields (**Scheme 2**).

The present paper describes the synthesis and resolution of 2,3-dihydro-2-*tert*-butyl-3-*N*-benzylquinazolin-4-one *rac*-**11** as a possible precursor of *cis*- and *trans*-2-aminocyclohexanecarboxylic acids. In this compound, it is important to mention that the *tert*-butyl group at C(2) adopts a pseudoaxial position, as shown by analysis of X-ray diffraction [10]-[12], and we would expect higher induction in asymmetric hydrogenation reaction: the ad- dition of the hydrogen on the *syn* face, leading to the exclusive formation of the only one diastereomer.

2. Results and Discussion

Synthesis of (±)-2,3-dihydroquinazolin-4(1*H*)-one *rac*-**11**.

Our research was focused in the preparation of starting material following the methodology previously reported by our group [11]-[13] in which a reaction between isatoic anhydride and benzylamine in ethyl acetate at 40˚C results in the corresponding aminobenzamide **10** with 90% yield. Next, cyclocondensation of **10** with pivalaldehyde in dichloromethane and *p*-toluenesulfonic acid monohydrate gives (±)-2,3,dihydro-4(1*H*)-quinazolinone *rac*-**11** at 86% yield (**Scheme 3**).

It is noteworthy that was necessary to protect the reaction from light source since this would suffer photoinduced elimination and hence reduces the yield of compound **11** [11].

The resolution was achieved by the preparation of the diastereomers **13a** and **13b** via condensation between the quinazolinone anion, formed with NaHMDS at −78˚C, and *N*-phthalyl-*L*-alanine chloride (*S*)-**12** as the resoluting agent [14]. Separation of the diastereomers was accomplished by flash chromatography from hexane/AcOEt (**Scheme 4**).

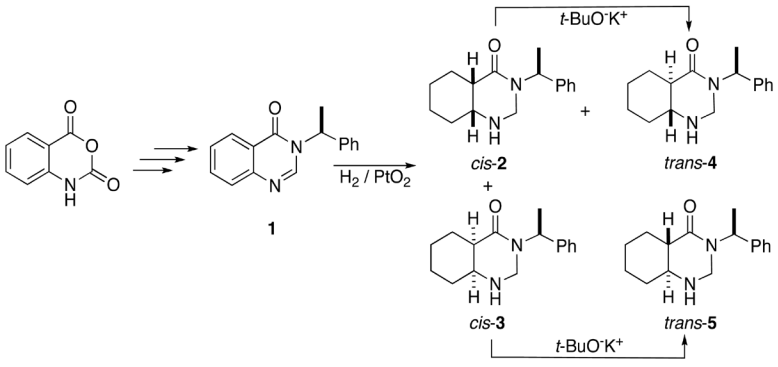
The assignment of the absolute configuration of the main products was achieved by X-ray diffraction analysis with the diastereomer **13a** (**Figure 1**). In this way, we were able to determine the relative configuration *S* at C(2) in the quinazolinone system for diastereomer **13a**, and consequently the opposite configuration for diastereomer **13b**.

It is important to mention that X-ray crystal-structure determinations used to elucidate the stereochemical outcome of **13a** revealed a pseudoaxial disposition of the *tert*-butyl group at C(2) (consequence of a powerful $A^{1,3}$ effect) [15]-[21], which could directs higher induction in addition toward the face opposite to this group in the hydrogenation reaction, leading to the exclusive formation of a single diastereomer.

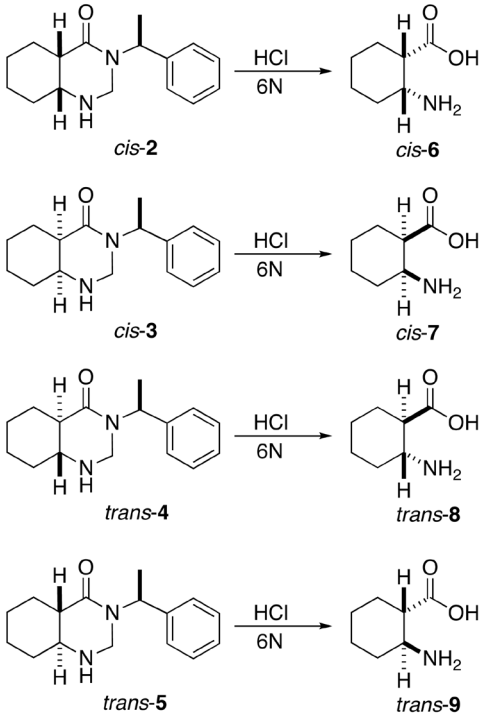
Finally, as shown in **Scheme 5**, conversion of diastereoisomers **13a** and **13b** to the enantiomerically pure quinazolinones (*R*)-**11** and (*S*)-**11**, was completed by hydrolysis with $Bu_4N^{+-}OH$ in 75 and 67% yield respectively.

3. Conclusion

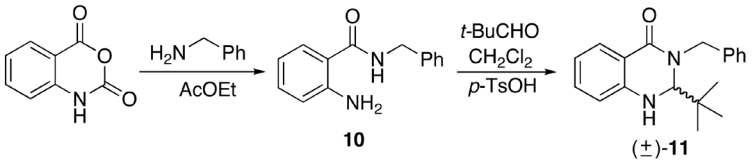
In conclusion, we present a new method for the preparation of enantiomerically pure quinazolinones (*R*)-**11** and (*S*)-**11**. The interest for these quinazolinones as intermediaries is given by their potential use in the formation of



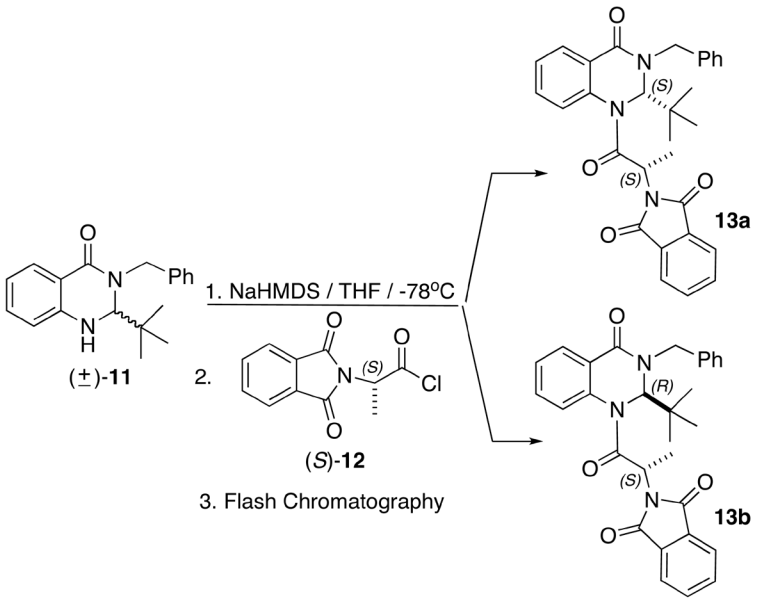
Scheme 1. Synthesis of octahydroquinazolinone diastereoisomers.



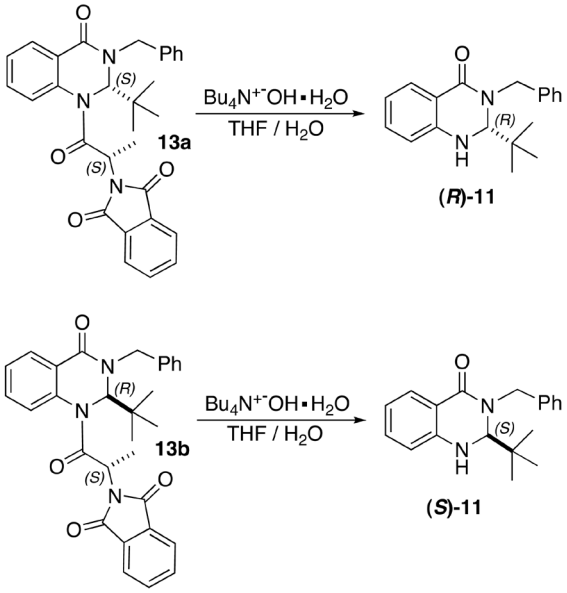
Scheme 2. Synthesis of *cis*- and *trans*-2-aminocyclohexanecarboxylic acid enantiomers.



Scheme 3. Synthesis of (±)-2,3.dihydro-4(1*H*)-quinazolinone *rac*-11.



Scheme 4. Synthesis of (*S*,*S*)- and (*R*,*S*)-diastereomers of quinazolinone (±)-11.



Scheme 5. Synthesis of enantiomerically pure quinazolinone (*R*)-11 and (*S*)-11.

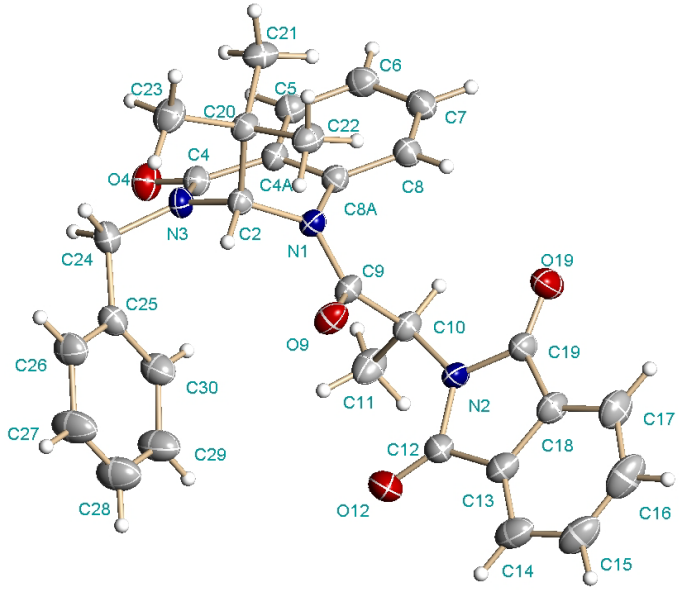


Figure 1. Structure and solid-state confirmation for 13a.

β-amino cyclohexancarboxylic acids. Further studies to explore these quinazolinones as new chiral auxiliaries in the synthesis of *β*-amino acids are in progress.

4. Experimental

TLC: Merck-DC-F254 plates; detection by UV light. Flash column chromatography [22]: Merck silica gel (0.040 - 0.063 mm). Mp: Mel-Temp apparatus; not corrected. Optical rotations were determined in a Perkin-Elmer 241 polarimeter at the sodium D-line. ^{1}H NMR spectra: Varian Oxford 400 MHz, ^{13}C NMR spectra: Varian Oxford 100 MHz. Chemical shifts (δ) in ppm downfield from the integral TMS reference; the coupling constants (J) in Hz. X-Ray: APEX-Bruker diffractometer. The structures were solved by direct methods using the program SHELXS [23]. Flasks, stirring bars and hypodermic needles used for the generation and reactions of organolithiums were dried for 12 h at 120˚C and al-

lowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.

4.1. Synthesis of 2-Amino-N-Benzylbenzamide (10)

A suspension of isatoic anhydride (10.0 g, 62 mmol) was treated with 1.0 equiv of benzylamine (6.7 mL, 62 mmol) in ethyl acetate according to published procedures [11]-[13]. The reaction mixture was warmed to 40˚C during 1 h. The solution was then concentrated under reduced pressure. The crude product was purified by flash chromatography. The benzamide **10** was produced 12.7 g (90%) as a white solid: mp 121˚C - 123˚C (Lit. [10] [12] mp 124˚C - 125˚C), ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 4.55 (d, J = 5.6 Hz, 2H, CH_2), 5.26 (br s, 2H, NH_2), 6.50 (br, 1H, NH), 6.59 (t, J_{ortho} = 7.4 Hz, 1H, C5-H), 6.65 (d, J_{ortho} = 8.4 Hz, 1H, C3-H), 7.18 (t, J_{ortho} = 7.8 Hz, 1H, C4-H), 7.24 - 7.35 (m, 6H, C6-H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 43.8, 115.8, 116.7, 117.4, 127.2, 127.5, 128.8, 132.4, 138.3, 148.8, 169.2. Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.29; H, 6.24; N, 12.38. Found: C, 74.28; H, 6.21; N, 12.38.

4.2. Synthesis of (±)-2,3-Dihydro-2-Tert-Butyl-3-Benzyl-4(1H)-Quinazolinone (Rac-11)

A solution of aminobenzamide **10** (6 g, 26.5 mmol) in 100 mL of CH_2Cl_2 was added 3.2 mL (31.8 mmol) of pivalaldehyde and then was added 0.12 g (2% by weight) of *p*-TsOH. The colorless solution was refluxed for 5 h. The reaction was monitored by TLC (hexane:ethyl acetate 7:3). The straw yellow solution was concentrated and the crude was purified by FC eluting with hexane:ethyl acetate 9:1 - 6:4 to afford 6.7 g (86%) of **11** as white solid. mp 140˚C - 143˚C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.87 (s, 9H, *t*-Bu), 3.92 (d, J = 15.6 Hz, 1H, CH_2), 4.24 (d, J = 3.2 Hz, 1H, C2-H), 4.40 (br d, J = 3.2 Hz, 1H, NH-1), 5.81 (d, J = 15.2 Hz, 1H, CH_2), 6.49 (d, J_{ortho} = 8 Hz, 1H, C8-H), 6.73 (t, J_{ortho} = 7.5 Hz, 1H, C6-H), 7.20 - 7.34 (m, 6H, C7-H y Ph), 7.85 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 1.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.6, 42.0, 51.4, 75.7, 113.3, 116.6, 118.1, 127.3, 127.4, 128.5, 128.7, 133.6, 137.4, 146.6, 163.8. Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.61; H, 7.46; N, 9.30.

4.3. Procedure for the Quinazolinone-11 Resolution

A solution of *rac*-**11** in THF was cooled to −78˚C before slowly adding 1.1 mol equiv. of NaHMDS in hexane (1.0 M). The resulting solution was stirred at −78˚C for 10 min and treated successively with the resolution agent (*N*-phthalyl-*L*-alanine chloride) [12] [24]. The mixture was stirred at the same temperature for 1 h and treated with saturated ammonium chloride solution and then with water. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered and evaporated to give the crude product. Purification of the crude product was accomplished by flash chromatography (hexane/AcOEt) and then by recrystallization from hexane/AcOEt yielding the corresponding diastereomer.

2-[(*S*)-1-[(*S*)-3-Benzyl-2-*tert*-butyl-4-oxo-3,4-dihydroquinazolin-1(2*H*)-yl]-1-oxopropan-2-yl]isoindoline-1,3-dione, (*S*,*S*)-**13a**.

44% Yield; mp 226˚C - 227˚C; $[\alpha]_D^{25}$ = + 439.5 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.806 (s, 9H, *t*-Bu), 1.20 (d, J = 7.6 Hz, 3H, CH_3), 4.00 (d, J = 14.8 Hz, 1H, CH_2), 5.65 (d, J = 14.8 Hz, 1H, CH_2), 5.70 (q, J = 8 Hz, 1H, CH), 5.79 (s, 1H, C2-H), 7.34 - 7.42 (m, 6H, C6-H y Ph), 7.60 (dt, J_{ortho} = 7.8 Hz, J_{meta} = 1.2 Hz, 1H, C7-H), 7.68 - 7.73 (m, 3H, Ph), 7.83 - 7.85 (m, 2H, Ph), 8.08 (dd, J_{ortho} = 7.6 Hz, J_{meta} = 1.6 Hz, 1H, C5-H); ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 13.5, 27.0, 39.3, 49.3, 52.1, 74.9, 123.2, 123.5, 125.3, 127.0, 128.2, 128.3, 128.9, 129.1, 132.1, 133.1, 133.3, 134.2, 137.1, 138.5, 162.5, 168.6, 170.2. HRMS: Calcd for $C_{30}H_{29}N_3O_4$: 495.2158 found: $[M + H]^+$ $C_{30}H_{30}N_3O_4$, 496.2252. X-Ray crystallographic structure in **Figure 1** [25].

2-((*S*)-1-((*R*)-3-Benzyl-2-*tert*-butyl-4-oxo-3,4-dihydroquinazolin-1(2*H*)-yl)-1-oxopropan-2-yl)isoindoline-1,3-dione, (*S*,*R*)-**13b**.

36% Yield; mp 110˚C - 112˚C; $[\alpha]_D^{25}$ = −224.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.66 (s, 9H, *t*-Bu), 1.57 (d, J = 7 Hz, 3H, CH_3), 4.07 (d, J = 14.4 Hz, 1H, CH_2), 5.10 (d, J = 13.6 Hz, 1H, CH_2), 5.24 (b, 1H, CH), 5.81 (s, 1H, C2-H), 6.94 (t, J_{ortho} = 7.4 Hz, 1H, C6-H), 7.13 (d, J_{ortho} = 8 Hz, 1H, C8-H), 7.22 - 7.37 (m, 5H, C7-H Ph), 7.46 (d, J_{ortho} = 6.8 Hz, 1H, C5-H), 7.51 (m, 5H, Ph) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 16.6, 27.1, 38.6, 47.2, 53.6, 76.0, 122.4, 123.2, 124.8, 126.3, 127.5, 128.2, 128.5, 129.0, 131.2, 132.9, 134.1, 137.2, 138.5, 162.7, 166.4, 168.9. HRMS: Calcd for $C_{30}H_{29}N_3O_4$: 495.2158 found: $[M + H]^+$ $C_{30}H_{30}N_3O_4$, 496.2235.

4.4. Procedure for Remotion of the Resolution Agent

To the appropriate diastereomer in THF was added at 0˚C an excess of Bu_4NOH solution under stirring for 12 h. The resulting mixture was concentrated at reduced pressure and purified by column chromatography (hex/AcOEt 50:50_0:10) to give the product as a white solid.

(*S*)-3-Benzyl-2-*tert*-butyl-2,3-dihydroquinazolin-4(1*H*)-one, (*S*)-**11**.

67% Yield. White solid, mp 153˚C - 154˚C. $[\alpha]_D^{25}$ = +68.72 (*c* 1.01, $CHCl_3$). Spectroscopy data were exactly identical to the racemic mixture.

(*R*)-3-benzyl-2-(*tert*-butyl)-2,3-dihydroquinazolin-4(1*H*)-one, (*R*)-**11**.

75% Yield. White solid, mp 152˚C - 153˚C. $[\alpha]_D^{25}$ = −68.87 (*c* 1.07, $CHCl_3$). Spectroscopy data were exactly identical to the racemic mixture.

Acknowledgements

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