

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*-annulated derivatives (**2** and **3**) could be epimerized in the presence of $t\text{-BuO}^-\text{K}^+$, 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 addition of the hydrogen on the *syn* face, leading to the exclusive formation of the only one diastereomer.

2. Results and Discussion

Synthesis of (\pm)-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 (\pm)-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 resolving agent [14]. Separation of the diastereomers was accomplished by flash chromatography from hexane/ AcOEt (Scheme 4).

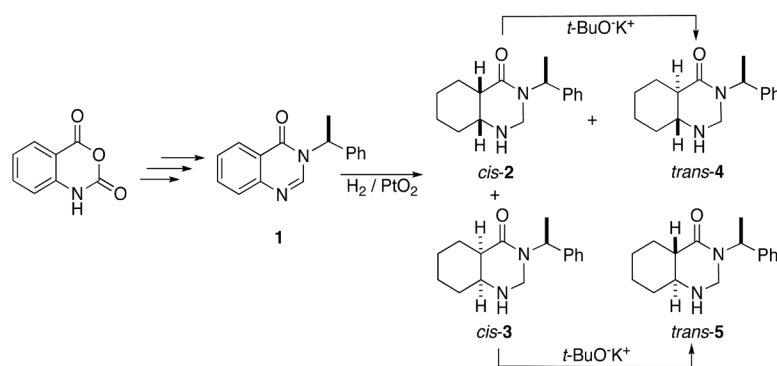
The assignment of the absolute configuration of the main products was achieved by X-ray diffraction analysis with the diastereomer **13a** (Figure 1). In this way, we were able to determine the relative configuration *S* at C(2) in the quinazolinone system for diastereomer **13a**, and consequently the 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 $\text{A}^{1,3}$ effect) [15]-[21], which could direct higher induction in addition toward the face opposite to this group in the hydrogenation reaction, leading to the exclusive formation of a single diastereomer.

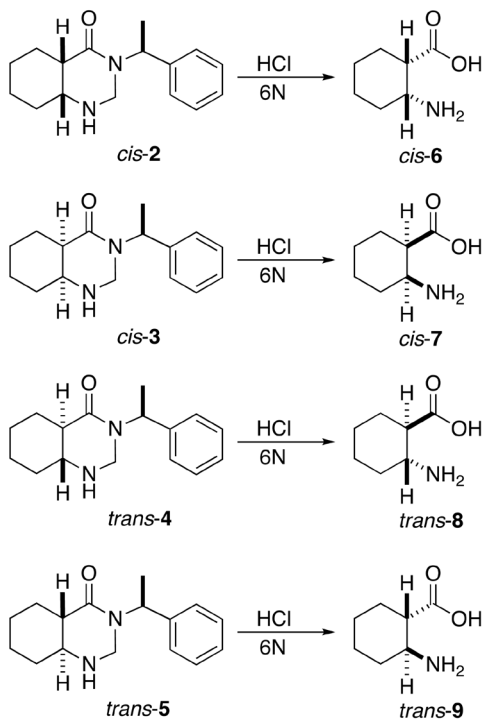
Finally, as shown in Scheme 5, conversion of diastereoisomers **13a** and **13b** to the enantiomerically pure quinazolinones (*R*)-**11** and (*S*)-**11**, was completed by hydrolysis with $\text{Bu}_4\text{N}^+\text{OH}$ in 75 and 67% yield respectively.

3. Conclusion

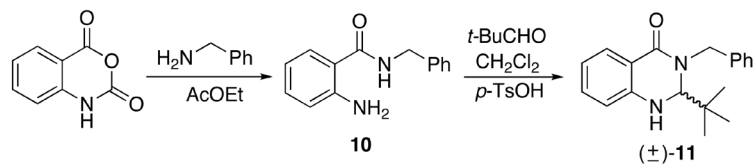
In conclusion, we present a new method for the preparation of enantiomerically pure quinazolinones (*R*)-**11** and (*S*)-**11**. The interest for these quinazolinones as intermediaries is given by their potential use in the formation of



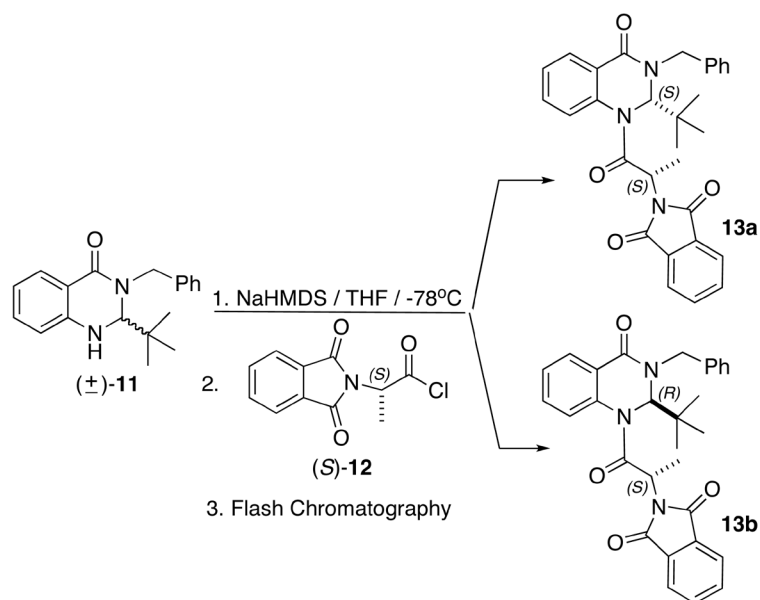
Scheme 1. Synthesis of octahydroquinazolinone diastereoisomers.



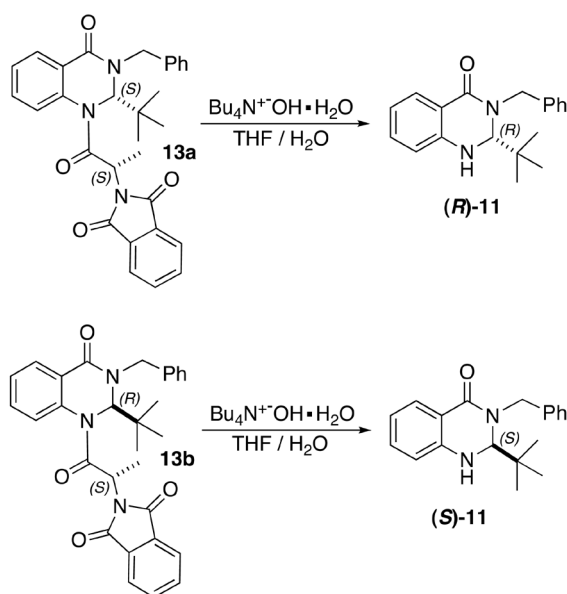
Scheme 2. Synthesis of *cis*- and *trans*-2-aminocyclohexanecarboxylic acid enantiomers.



Scheme 3. Synthesis of (±)-2,3-dihydro-4(1H)-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.

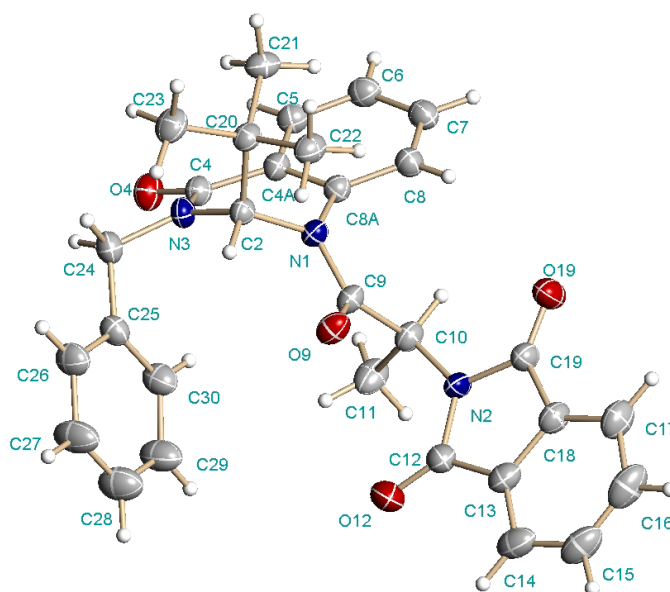


Figure 1. Structure and solid-state confirmation for 13a.

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. ^1H 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 CaSO₄. 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), ¹H NMR (CDCl₃, 400 MHz): δ (ppm): 4.55 (d, *J* = 5.6 Hz, 2H, CH₂), 5.26 (br s, 2H, NH₂), 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); ¹³C NMR (CDCl₃, 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 C₁₄H₁₄N₂O: 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 CH₂Cl₂ 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. ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.87 (s, 9H, *t*-Bu), 3.92 (d, *J* = 15.6 Hz, 1H, CH₂), 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, CH₂), 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); ¹³C NMR (CDCl₃, 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 C₁₉H₂₂N₂O: 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 CH₂Cl₂. The combined extracts were dried (Na₂SO₄), 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; [α]_D²⁵ = +439.5 (*c* 1.04, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.806 (s, 9H, *t*-Bu), 1.20 (d, *J* = 7.6 Hz, 3H, CH₃), 4.00 (d, *J* = 14.8 Hz, 1H, CH₂), 5.65 (d, *J* = 14.8 Hz, 1H, CH₂), 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); ¹³C 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 C₃₀H₂₉N₃O₄: 495.2158 found: [M + H]⁺ C₃₀H₃₀N₃O₄, 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; [α]_D²⁵ = -224.3 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.66 (s, 9H, *t*-Bu), 1.57 (d, *J* = 7 Hz, 3H, CH₃), 4.07 (d, *J* = 14.4 Hz, 1H, CH₂), 5.10 (d, *J* = 13.6 Hz, 1H, CH₂), 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) ¹³C NMR (100 MHz, CDCl₃) 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 C₃₀H₂₉N₃O₄: 495.2158 found: [M + H]⁺ C₃₀H₃₀N₃O₄, 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 Bu₄NOH 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. [α]_D²⁵ = +68.72 (*c* 1.01, CHCl₃). 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. [α]_D²⁵ = -68.87 (*c* 1.07, CHCl₃). Spectroscopy data were exactly identical to the racemic mixture.

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References

- [1] Zhang, Z., Lu, H., Yang, S. and Gao, J. (2010) Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-Ones by Three-Component Coupling of Isatoic Anhydride, Amines, and Aldehydes Catalyzed by Magnetic Fe₃O₄ Nanoparticles in Water. *Journal of Combinatorial Chemistry*, **12**, 643-646. <http://dx.doi.org/10.1021/cc100047j>
- [2] Wu, H., Xie, X. and Liu, G. (2010) Parallel Solution Phase Synthesis of 3,6,7-4(3*H*)-Quinazolinones and Evaluation of Their Antitumor Activities against Human Cancer. *Journal of Combinatorial Chemistry*, **12**, 346-355. <http://dx.doi.org/10.1021/cc900173s>
- [3] Bowman, W., Elsegood, M., Stein, T. and Weaver, G. (2007) Radical Reactions with 3*H*-Quinazolin-4-Ones: Synthesis of Deoxyvasicinone, Mackinazolinone, Luotonin A, Rutaecarpine and Tryptanthrin. *Organic & Biomolecular Chemistry*, **5**, 103-113. <http://dx.doi.org/10.1039/b614075k>
- [4] Kshirsagar, U., Puranik, V. and Argade, N. (2010) Total Synthesis of Proposed Auranthine. *Journal of Organic Chemistry*, **75**, 2702-2705. <http://dx.doi.org/10.1021/jo100400z>
- [5] Mhaske, S. and Argade, N. (2006) The Chemistry of Recently Isolated Naturally Occurring Quinazolinone Alkaloids. *Tetrahedron*, **62**, 9787-9826. <http://dx.doi.org/10.1016/j.tet.2006.07.098>
- [6] Zeng, F. and Alper, H. (2010) One-Step Synthesis of Quinazolino[3,2-*a*]Quinazolinones via Palladium-Catalyzed Domino Addition/Carboxamidation Reactions. *Organic Letters*, **12**, 3642-3644.
- [7] Witt, A. and Bergman, J. (2000) Synthesis and Reactions of Some 2-Vinyl-3*H*-Quinazolin-4-Ones. *Tetrahedron*, **56**, 7245-7253. [http://dx.doi.org/10.1016/S0040-4020\(00\)00595-0](http://dx.doi.org/10.1016/S0040-4020(00)00595-0)
- [8] Larksarp, C. and Alper, H. (2000) Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Heterocumulenes: Regioselective Preparation of 4(3*H*)-Quinazolinone Derivatives. *Journal of Organic Chemistry*, **65**, 2773-2777. <http://dx.doi.org/10.1021/jo991922r>
- [9] Wang, M., Dou, G. and Shi, D. (2010) Efficient and Convenient Synthesis of Pyrrolo[1,2-*a*]Quinazoline Derivatives with the Aid of Tin(II) Chloride. *Journal of Combinatorial Chemistry*, **12**, 582-586. <http://dx.doi.org/10.1021/cc100062e>
- [10] Priego, J., Flores, P., Ortiz-Nava, C. and Escalante, J. (2004) Synthesis of Enantiopure *Cis*- and *Trans*-2-Aminocyclohexane-1-Carboxylic Acids from Octahydroquinazolin-4-Ones. *Tetrahedron: Asymmetry*, **15**, 3545-3549. <http://dx.doi.org/10.1016/j.tetasy.2004.08.032>
- [11] Cabrera-Rivera, F., Ortiz-Nava, C., Escalante, J., Hernandez-Perez, J. and Ho, M. (2012) Photoinduced Elimination in 2,3-Dihydro-2-*Tert*-Butyl-3-Benzyl-4(1*H*)-Quinazolinone: Theoretical Calculations and Radical Trapping Using TEMPO Derivatives. *Synlett*, **23**, 1057-1063. <http://dx.doi.org/10.1055/s-0031-1290492>
- [12] Escalante, J., Flores, P. and Priego, J. (2004) Synthesis of 2,3-Dihydro-4(1*H*)-Quinazolinones. *Heterocycles*, **63**, 2019-2032. <http://dx.doi.org/10.3987/COM-04-10130>
- [13] Escalante, J., Ortiz-Nava, C., Flores, P., Priego, J. and Garcia-Martinez, C. (2007) Synthesis, NMR and Crystallographic Studies of 2-Substituted Dihydroquinazolinones Derived from (*S*)-Phenylethylamine. *Molecules*, **12**, 173-182. <http://dx.doi.org/10.3390/12020173>
- [14] Escalante, J. and Gonzalez-Tototzin, M. (2003) Synthesis, Resolution and Absolute Configuration of *Trans*-4,5-Diphenyl-Pyrrolidin-2-One: A Possible Chiral Auxiliary. *Tetrahedron: Asymmetry*, **14**, 981-985.

[http://dx.doi.org/10.1016/S0957-4166\(03\)00097-1](http://dx.doi.org/10.1016/S0957-4166(03)00097-1)

- [15] Seebach, D., Lamatsch, B., Amstutz, R., Beck, A., Dobler, M., Egli, M., Fitzi, R., Gautschi, M., Herradon, B., *et al.* (1992) Structure and Reactivity of Five- and Six-Ring N,N-, N,O-, and O,O-Acetals: A Lesson in Allylic 1,3-Strain (A1,3 Strain). *Helvetica Chimica Acta*, **75**, 913-934. <http://dx.doi.org/10.1002/hlca.19920750326>
- [16] Murer, P., Rheiner, B., Juaristi, E. and Seebach, D. (1994) Enantioselective Synthesis of β -Amino Acids. 5. Stereoselective Reaction of Chiral Pyrimidinone Enolates with Aldehydes. *Heterocycles*, **39**, 319-344. [http://dx.doi.org/10.3987/COM-94-S\(B\)35](http://dx.doi.org/10.3987/COM-94-S(B)35)
- [17] Seebach, D., Boog, A. and Schweizer, W.B. (1999) EPC-Synthesis of β -Amino Acid Derivatives through Lithiades Hydroxypyrimidines. *European Journal of Organic Chemistry*, **1999**, 335-360.
- [18] Ramirez-Quiros, Y., Balderas, M., Escalante, J., Quintana, D., Gallardo, It., Madrigal, D., Molins, E. and Juaristi, E. (1999) X-Ray Crystallographic Study of Substituted Perhydroxypyrimidinones. Extreme Changes in Ring Conformation. *Journal of Organic Chemistry*, **64**, 8668-8680. <http://dx.doi.org/10.1021/jo991297q>
- [19] Johnson, F. (1968) Allylic Strain in Six-Membered Rings. *Chemical Reviews*, **68**, 375-413. <http://dx.doi.org/10.1021/cr60254a001>
- [20] Hoffmann, R. (1989) Allylic 1,3-Strain as a Controlling Factor in Stereoselective Transformations. *Chemical Reviews*, **89**, 1841-1860. <http://dx.doi.org/10.1021/cr00098a009>
- [21] Broeker, J., Hoffmann, R. and Houk, K. N. (1991) Conformational Analysis of Chiral Alkenes and Oxonium Ions: *Ab Initio* Molecular Orbital Calculations and an Improved MM2 Force Field. *Journal of the American Chemical Society*, **113**, 5006-5017. <http://dx.doi.org/10.1021/ja00013a041>
- [22] Still, W., Kahn, M. and Mitra, A. (1978) Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *Journal of Organic Chemistry*, **43**, 2923-2925. <http://dx.doi.org/10.1021/jo00408a041>
- [23] Sheldrick, G.M. (1998) SHELX97, Programs for Crystal Structure Analysis, Release 97-2. Institute for Inorganic Chemistry der Universität, Göttingen.
- [24] Camps, P., Perez, F., Soldevilla, N. and Borrego, M. (1999) (R)- and (S)-3-Hydroxy-4,4-Dimethyl-1-Phenyl-2-Pyrrolidinone as Chiral Auxiliaries in the Enantioselective Preparation of α -Amino Acids. *Tetrahedron: Asymmetry*, **10**, 493-509. [http://dx.doi.org/10.1016/S0957-4166\(99\)00018-X](http://dx.doi.org/10.1016/S0957-4166(99)00018-X)
- [25] Crystallographic Data Is Deposited at Cambridge Crystallographic Data Center (CCDC: No. 900252).